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PRESENT DAY CONCEPTION OF PROTAMINE ZINC INSULIN AND GLOBIN INSULIN WITH ZINC

Special References to Insulin Hypoglycemia and "Insulin Mixtures."

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When the slow acting insulin—protamine zinc—was first introduced into diabetic therapy physicians eliminated the necessity of multiple injections. It enabled many patients to "control" their diabetes with one daily injection of protamine zinc alone or in combination with plain insulin—but not without hypoglycemia reactions.

The marked difference between the protamine and plain insulin rate of action was first realized by the author soon after the development and general use of protamine zinc insulin.[1] It then became apparent that this new insulin compound, protamine zinc insulin, though possessing certain advantages over the unmodified or regular insulin, had marked limitations as well as marked disadvantages. 1. Because of its slow absorption and action, protamine zinc insulin cannot control the hyperglycemia of the high carbohydrate diets or such diabetic complications as acidosis, infection or gangrene. 2. Protamine zinc insulin may involve the physician's giving too frequent injections or too large doses in his effort to reduce quickly the blood sugar and thus producing cumulative effects having such serious consequences as a continuous mild hypoglycemia reaction or even a severe and fatal one. 3. Patients aware of its unfavorable action—such as its cumulative effects—may become fearful of its slow acting hypoglycemic reaction, may fall into a mild mental confusion or into unconsciousness without much warning. 4. Prolonged insulin effect may continue when not much insulin action is desired.

Our subsequent studies of 1,093 diabetics revealed that in 50% of the cases it was necessary to combine plain insulin with protamine zinc insulin so as to help reduce the increased blood sugar caused by the high carbohydrate diets. This group of 50% comprised those patients who required plain insulin with protamine zinc insulin for one meal, either breakfast or supper, and those who in addition to these combined insulins required plain insulin at another meal, i. e., either for breakfast or supper. In none of the patients was it necessary after the stabilization or "control" of their diabetes to give insulin for lunch (midday meal). The age of the patients varied from 6 to 84 years; total daily dose of both insulins varied from 24 to 200 units. In some instances the dose was higher, even totalling 1350 units for a few weeks in one case.

However, in neither groups comprising the 50% were the patients completely free from hypoglycemic symptoms. We observed that a few patients developed a peculiar dread of protamine zinc insulin reaction. They often dreaded sleeping alone because of the frequency of early morning reactions. It was not uncommon for patients to awaken with tingling sensations around the mouth or on the fingers, or in a mental stupor to be succeeded by a profound insulin coma.

However, there were patients, 16% of the cases, whose slight fluctuation of the blood sugar was "apparently controlled" by one injection of protamine. The dose of the insulin varied from 10 units to 80 units. The age of the patients ranged from 28 to 85 years. Although no attempt was made to change to plain insulin, a few of the patients in this group could have been controlled by plain insulin.

In the younger group, however, it was not possible in most instances to control ade-

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quately the blood sugar level without combining the protamine zinc with plain insulin. This group appeared to be more dangerous because the physician in prescribing one injection of the protamine insulin was often satisfied by a fasting blood sugar within the so-called "normal range" of 140 mg. It was not uncommon to observe protamine zinc insulin patients with a blood sugar of 140 mg. who looked well with no suspicious hypoglycemic symptoms but who developed acute insulin coma or shock in early morning hours, or at intervals when the shock is least expected.

The same hypoglycemia reactions occurred when protamine zinc insulin was combined with plain insulin. Thus, to cite one of the many cases, a diabetic male, aged 8 years, was taking 20 units of protamine zinc insulin plus 14 units of plain insulin for breakfast and no insulin for lunch or supper. He appeared to be controlled with this insulin dose, for a period of 2 months maintaining a fasting blood sugar of 140-180 mg. Upon rising one morning after partly dressing himself, he walked into the back yard of his home and fell into a pool of water. Fortunately he was immediately rescued by his mother who summoned the doctor. The child responded immediately to glucose administration. Later he had no recollection of having dressed himself.

It is not uncommon to see patients on protamine zinc insulin develop such signs of mental impairment as lapse of memory, forgetfulness, impaired or blurred vision, loss of appetite, frequent headache, morning nausea and vomiting, weakness in the legs, slight to extremely marked fatigue and increased irritability. In some instances the protamine zinc insulin shock may precipitate severe vascular damage or sudden death. This danger becomes more serious in the elderly patients with extensive cardiovascular sclerosis.

To cite a case, worthy of note, of mental impairment resulting from protamine zinc insulin shock: a male, aged 39 years who has had diabetes for 19 years, taking 60 units of protamine for breakfast. The patient was subject to marked fatigue, tiredness, morning nausea, frequent vertigo spells, headaches, and blurred vision which occurred at infrequent intervals throughout the day and lasted at times an hour or longer. It was not uncommon for him after conversing with a person for an hour or more to find himself regain consciousness in a hospital, and not recall his conversation with the person. As a result of the protamine zinc insulin reaction, he became fearful of any slight disturbance of his physical equilibrium as a possible sign of the onset of insulin shock or coma. To counteract this fear he ate candy or some form of carbohydrate, even though in many instances the disturbances were not signs or symptoms of the onset of insulin shock. This, of course, upset his diet balance. The patient at present suffers from memory impairment, depression, suicidal intent, irritability. As a result of his present mental affection he is unable to hold his executive position in a large corporation.

Thus, to cite one of a few examples of marked vascular damage resulting in the death of the patient from protamine zinc insulin shock is the case of a female diabetic, aged 72 years, who was taking 15 units of protamine insulin for 1 month who suddenly developed a left sided hemiplegia 2 days before admission to my service. The laboratory and physical signs of suspected "acidosis" caused the physician to give the patient 50 units of protamine; 15 hours later, 40 units more of protamine. Upon admission to our service the patient was comatose, with a blood sugar 93 mgs. CO_2 54 vols. per. cent. Glucose and other forms of therapy failed to arouse the patient. Electrocardiogram suggested lateral myocardinal infarction. Unfortunately, post-mortem was not obtained, but death was perhaps precipitated by insulin shock, bringing about cerebral thrombosis or hemorrhage, resulting in left sided hemiplegia, hypertensive cardio-vascular disease with decompensation.

Another important reaction from protamine zinc insulin even though combined with plain insulin is that some patients are able to have low blood sugar levels at irregular intervals with no apparent symptoms. These low blood sugar levels persisting at irregular intervals over long periods may slowly or suddenly produce permanent cerebral damage resulting in attacks of convulsions, and not infrequently in the death of the patient.

To cite a case: a young male aged 33 years,

who has had diabetes for 18 years with pulmonary tuberculosis, was brought into the hospital by the police in a comatose condition after having been found unconscious on a vacant lot. His insulin dose before accident was 15 units of plain and 18 units of protamine for breakfast, and 10 units of plain insulin for supper. On admission his blood sugar was 52 mg., and carbon dioxide combining power of the blood plasma was 40 mg. In spite of therapy he never regained consciousness and died 5 days after admission to hospital.

Another not uncommon instance is that of a young man aged 26 years, whose diabetes of 3 years duration was apparently well controlled on 26 units of plain insulin and 26 units of protamine zinc insulin for breakfast. The patient had his regular lunch at 12:30 P. M. He remembered reading a newspaper about 5:30 P. M., after which he suddenly became unconscious, with convulsive seizures when brought to the hospital. At the hospital, after regaining consciousness from intravenous glucose, a severe bleeding laceration over forehead was found, probably the result of a fall. Since this accident the patient has had weakness in left arm and hand with numbness and slight impairment of speech. He fears travelling alone without his wife because of his previous protamine insulin shocks.

Immediate and Latent Effects of Protamine Zinc Insulin Hypoglycemia

The increasing, unfavorable reactions of protamine zinc insulin observed by the writer since its inception in diabetic therapy have been disappointing and at times alarming. In spite of the therapeutic value of protamine insulin, the reactions vary from those of plain or ordinary insulin hypoglycemia, i. e., the patients on protamine zinc insulin may have a low blood sugar (hypoglycemia level) for a short interval without apparent signs or symptoms. What the ultimate effects of protamine zinc insulin hypoglycemia, occurring at infrequent intervals with variable duration, will have upon the patients has already been observed on the neurological, cardiovascular and endocrine systems, as well as the fatal results. A review of the highlights of the literature will reveal that the author is not alone in his observations.

The editor[2] of the *Journal of the American Medical Association* makes note of the hope that was entertained for the newer protamine zinc insulin—that it would be less toxic, and less provocative of hypoglycemic reactions over the older unmodified insulin in its effects. This hope, far from being fulfilled, was shattered by innumerable reports of its unfavorable reactions even to the point of being a contributing factor in the death of a diabetic patient. The editor[3] of "The British Medical Journal," in agreement with the editor of The *Journal of the American Medical Association* about the seriousness of protamine zinc insulin hypoglycemia says: "But the increased incidence of grave hypoglycemia since the introduction of delay....action protamine insulin is understandable and merits discussion.

"The effect of a reduction of blood sugar falls on the central nervous system, and the mechanism and pathological results are becoming known. Glucose is the main if not the only fuel of the brain and its metabolism and vital processes stop without it. If the blood sugar supply is cut off by insulin for a few hours (say 4 to 8) irreversible nerve cell changes may occur which cannot be removed by the restoration of the blood sugar...fortunately an extremely rare event."

(a) Effects on Neurological System

Klein and Ligsterink[4] report damage of the brain in patients with diabetes who required large doses of insulin and in whom hypoglycemia reactions was a continuous event which could not be avoided. They describe the close resemblances of these insulin reactions in diabetic patients to those of non-diabetic patients given Sakel's therapy. They are of the opinion that protamine zinc insulin, in keeping the blood sugar level at abnormally low levels for many hours, leads to dangerous effects upon the central nervous system and speak of the rather high percentage of fatal effects in protamine zinc insulin treated diabetic patients. The longer the insulin coma, the greater the cerebral damage. In their observation they report 2 cases of serious hypoglycemic damage to the brain: one, a diabetic patient, aged 22 years, physically sound,

treated with regular and protamine zinc insulin, was in hypoglycemic coma for many days. The diabetic's hypoglycemia syndrome resembled the other patient's, a schizophrenic with extensive neurologic disturbances. The intellectual level of the diabetic was that of a complete idiot. Kepler[5] emphasizes the danger of hypoglycemia attacks producing permanent pathological changes to the central nervous system. He cites a case of a patient having recurring protamine zinc insulin reactions admitted to the hospital with serious signs of memory defect.

Sherrill and McKay's[6] post-mortem studies of a series of animals treated with overdoses of protamine zinc insulin conclude that long continued hypoglycemia affects the metabolism of the brain in an adverse manner and gives rise to degenerative change. They found evidence of permanent functional damage to the brain—permanent sensory and motor disturbances as a result of prolonged hypoglycemia. In dogs, after long-continued periods of hypoglycemia, they observed impairment of complete lack of vision or hearing, disturbances of the emotional complex, incoordination, spasticity and even paralysis. They concluded from these observations that care should be taken in preventing unnecessary hypoglycemia reaction, and that shock that results from insulin for therapeutic purposes should be maintained for as short a time as possible. Gellhorn[7] concludes from his studies that hypoglycemia affects the central nervous system in a way similar to that of oxygen deficiency—both reduce the rate of oxidation. It is believed the brain is dependent upon a constant supply of carbohydrate from the blood and that hypoglycemia greatly increases the sensitivity of the central nervous system to oxygen deficiency. Himwich and his co-workers[8] have observed in their studies of cerebral metabolism of patients during insulin shock therapy a diminution of oxygen utilization during coma from 7.09 volumes per cent to 3.07 volumes per cent, an approximately 55 per cent diminished metabolism of the brain. They are of the opinion that the depressed cerebral metabolism and the coma are the direct result of carbohydrate absence —diminished blood sugar resulting from insulin injection, since carbohydrate is the only one foodstuff oxidized by the brain. However, they claim that the brain does not suffer from lack of oxygen during hypoglycemia. In fact, they are of the opinion that the oxygen content of the brain may be increased due to the diminished utilization of the gas.

Cobb[9] is of the opinion that during coma and convulsions, the result of insulin hypoglycemia therapy in mental cases, there is a probable destruction of cerebral nerve cells. Based upon physiological and pathological findings it was strongly suggestive to him that the cerebrum is partially asphyxiated for long periods during treatment. He is also of the opinion that there may be many cells lost without causing mental impairment. Allan and Crommelin[10] claim that hypoglycemia may cause death or permanent disability from cerebral damage. They described the case of a 6-year-old girl, who was receiving 25 units of protamine zinc insulin daily before breakfast, who developed a serious insulin reaction —unconsciousness with twitching and convulsions and stupor for 3 days. When she was aroused, she had developed right sided hemiplegia and aphasia. These complications, although less pronounced, persisted upon her discharge from the hospital. From the last report of her case, fifteen months since the onset of hypoglycemia reaction, she was still handicapped by aphasia, and with epileptic seizures occurring at intervals. They ascribed the organic cerebral changes in this case to the prolonged hypoglycemia reactions of the protamine insulin with severe prognosis.

Schizophrenic patients treated with protamine zinc insulin by Reese and Vander Veer[11] were returned to the use of regular insulin. They found the danger of after-shock was greater, and epileptiform shocks were more frequent with protamine zinc insulin. They also observed that it was impossible to produce uniform shock dose with protamine zinc insulin because the effects of equal doses were not always the same and the dose had to be constantly varied.

Since the store of carbohydrate in the brain is small, Himwich and Fazenkas[12] claim there is utilization during profound hypoglycemia which supplies material for oxidation. The central nervous system ceases to function when there is no available carbohydrate in the

blood or in the brain for oxidation. When the brain, according to these investigators, is denied its chief source of energy, glucose, there is a diminished cerebral consumption causing impairment of normal function which has deepseated effects on cerebral physiology.

Malamud and Grosh[13] in describing a case of chronic hypoglycemia caused by islet cell adenoma, correlate the clinical course of convulsions, psychotic manifestations, and organic dementia with advancing destruction of the cerebral cortex and basal ganglia. This diffuse degeneration of the brain is interpreted by them to be due to a direct toxic effect of insulin on the parenchyma. Baker and Lafkin's[14] post-mortem observations of the human brain of hypoglycemia cases found scattered irregularly throughout the brain tiny hemorrhages which were more prevalent in the patients who had the worse convulsive attacks. Berman and Riess'[15] animal studies of the effect of insulin shock, point to a more severe impairment of the newer and less overstrained habits—impairment of learning of a recently acquired alley or elevated maze habit with no impairment of older habits either in the elevated or alley maze.

One of Himwich and Fazenkas'[12] explanations for the diminished circulatory rate through the brain during hypoglycemia is the reduction of the heart rate to 50 or 25 per cent of its normal value. They are of the opinion that the slow heart rate caused by increased irritability of the vagus center in the medulla is a signal of inadequate metabolism of the brain—diminished cerebral utilization of glucose and oxygen. However, the heart rate may again become more rapid because of the effects of the sympathetic system. It is during this latter phase that the cardiac criterion is lost and the animal may die of respiratory failure, since the central nervous system is bereft of its necessary carbohydrate.

Drysdale[16] reports two cases. One, a 14-year-old girl, because of the development of acute hysteria was shifted from protamine zinc to regular insulin. She recovered while in the hospital. The other patient, a white, 19-year-old male, developed acute dementia praecox while on protamine zinc insulin, for which asylum commitment was required although his diabetes, as claimed by Drysdale, was adequately controlled. During the course of his insulin therapy previous to the mental condition, 60 units of protamine insulin and 10 units of regular insulin were given. Even though his postprandial blood sugar was 37 mg., no hypoglycemia symptoms were noted. Drysdale raises the question of protamine insulin therapy in diabetes as a precipitating factor in the psychosis of the two above patients, although he is not sure there is adequate evidence to support such a contention.

Wilder and Wilbur[17] in describing symptoms of hypoglycemia produced by protamine insulin, claim that the blood sugar level falls so gradually that the adrenal glands seem not to be aroused, thereby not producing the usual symptoms of insulin shock to which the physician is accustomed. Instead, the only symptoms of hypoglycemia may be of cerebral origin—drowsiness, headache, nausea and fatigue, and since such symptoms often resemble acidosis one may confuse it with this complication. If vomiting has occurred with the hypoglycemia reaction of protamine insulin, it not infrequently complicates the picture. Even though symptomless, Wilder speaks of long continued hypoglycemia as not without peril. In severe diabetes he felt it to be safer to permit the intermittent excretion of some sugar, and for the most part he found the patients felt better and stronger.

(b) EFFECTS OF HYPOGLYCEMIA ON THE CARDIO-VASCULAR SYSTEM

The seriousness of hypoglycemia, as stressed by Soskin and his associates,[18] who observed myocardial impairment from insulin hypoglycemia, emphasizes the danger of protamine zinc insulin hypoglycemia upon the cardio-vascular system. Their results were similar to those seen in elderly diabetics with cardio-vascular disease when insulin was administered in therapeutic doses in amounts not causing hypoglycemia. The myocardial impairment caused by insulin was also obtained with low carbohydrate diets and was manifested by complaints of subjective distress in their patients. Blake's[19] survey of seventy-four non-diabetic patients suffering from acute coronary occlusion found 20 per cent to have hyperglycemia or glycosuria shortly after the acute onset of the occlusion.

However, at the end of their convalescence period, the blood sugar returned to normal, or the urine became sugar free without treatment. This latter observation of the sugar metabolism is perhaps indicative that some compensatory action has been precipitated by the acute coronary occlusion, as evidenced in a case with a fasting hyperglycemia of 244 mg. per 100 cc., whereas 110 days after the onset of the coronary attack the fasting blood sugar was 86 mg. and urine negative for glucose. It is apparent that if such a case were complicated by diabetes resulting in a higher blood sugar level and a greater glycosuria, the physician would be tempted to give large doses of insulin or markedly reduce the carbohydrate intake of the diet and bring about a serious reaction or even sudden death. That such catastrophes have occurred is noted by Gigon's[20] case report of a patient suffering from diabetes and acute congestive heart failure who died following the injection of insulin. Blake[19] is of the opinion that high blood sugar is beneficial and not deleterious to cardiac patients, especially the ones with anginal type of cardiac distress.

Explanation by some investigators for the greater content of cardiac glycogen in diabetics than in the normal is that the condition may be due to decreased oxidation of glucose, which is in accord with the disturbed carbohydrate oxidation in diabetes, or to a lowered efficiency of the heart in diabetes.[21] Goldman's[22] observations have revealed that large doses of protamine zinc insulin, though causing only moderate hypoglycemia, produced marked electrocardiographic changes. These electrocardiographic changes he feels are brought on by the deviation of carbohydrate oxidation induced by excessive insulin or absence of available carbohydrate, or by both. He feels that the fundamental change which became evident in altered electrical manifestations was in the chemical dynamics of myocardial activity. After cessation of all insulin, in spite of the absence of hypoglycemic reaction, the changes receded after a period of weeks or months.

Sherrill[23] gives special warning about the use of protamine zinc insulin in the treatment of elderly diabetics with potential or actual coronary and heart disease because of the seriousness of prolonged hypoglycemia. As to the hypoglycemia reactions brought on by protamine zinc insulin, the symptomatic as also the objective manifestations are distinctly different from the ordinary insulin. The patients may have a blood sugar of 59 mg. and still be oblivious as to its existence and not be disturbed in any way. However, the usual symptoms may be drowsiness, vague, mental confusion, lassitude, hunger; or the first symptom may be when the patients lapse into a stupor or unconsciousness. Nevertheless, sweating, palpitation, and tremor are rare. Even in the severe reactions, when revived by glucose, the patient may relapse into another violent hypoglycemia reaction. Walther and Ammon[24] are of the opinion that the injections of small amounts of foreign protein, of which protamine is one, having a molecular weight of 1,560, over periods of years must not be ignored as harmless unless further investigations are made. They feel that late injuries, especially to the vascular system by permanent injections of foreign protein, may be produced. They are of this opinion because fatal shocks have been observed when the first protein containing insulin preparations were given by the medical profession, even though anaphylactic shock in man is hardly possible.

(c) ENDOCRINE SYSTEM

Mirsky and his associates'[25] observations, in accord with the results of other investigators[26] "that insulin administration results in a decrease in the administration of insulin by the islet tissue," have concluded that the prolonged administration of protamine zinc insulin accentuates this latter condition to such a degree that "disuse atrophy" of the pancreas results. This effect would bring about a reduction of the insulin production and content of the normal islet tissue with a possibility of producing permanent diabetes (permanent hyperglycemia and glycosuria). Based upon these results they advised against the use of protamine zinc insulin as a prophylactic measure in man even though a beneficial effect is obtained in diabetes mellitus.

Mirsky and his associates'[25] studies were substantiated by the work of Rosenbaum and his co-workers.[27] Following the administration of insulin these latter investigators pro-

voked diabetic response to glucose tolerance in a group of non-diabetic subjects. They found that the normal carbohydrate response returned within 36 hours after crystalline insulin and not within 63 hours after the last dose of protamine. They inferred that continued action of protamine zinc insulin over the 3-day period was the cause for the failure of the glucose tolerance curve to return to normal within 3 days of stopping protamine zinc insulin. They expressed the opinion that since insulin can produce a delay in oxidation of carbohydrate in normal subjects upon a liberal diet, similar effects in diabetics seem possible. Based upon clinical observations they stressed the importance of avoiding insulin overdosages, since carbohydrate tolerance may be reduced by it. They advise carbohydrate supply at the interval when insulin effect is maximal, as well as bedtime feeding in protamine insulin patients. One of their explanations for the reduced carbohydrate tolerance is the possible suppression of the pancreas' insulin secreting mechanism. This conclusion is consistent with Best and Baist's[26] observation that the insulin content of the pancreas is diminished under insulin therapy. Prolonged protamine zinc insulin therapy over a period of years is not to be ignored as a possible explanation for the production of atrophy of the pancreas.

A patient on the Metabolic Service, aged 33 years, white, male, who was known to have had diabetes for 18 years and who required 30 units of protamine zinc insulin and 15 units of ordinary insulin for breakfast and 10 units of ordinary insulin for supper, was found in a comatose state in a vacant lot and brought to the hospital with a blood sugar of 52 mg. per 100 cc., and CO_2 40 vol. per cent. He died 6 days after admission to the hospital. Post-mortem examination revealed an extremely soft pancreas, weighing 25 gms. Histologically, hyalinosis of the islets, and autolysis was found.

(d) FATAL EFFECTS

Margolin[28] reports a fatal case of hypoglycemia from protamine insulin. Others[29] describe difficulties with protamine zinc insulin: "diurnal glycosuria...necessity for supplementary injections of regular insulin ... serious, even fatal reactions and often ... the abandonment of protamine zinc insulin in many cases in which its aid would have been most welcome." Protamine zinc insulin hypoglycemia coma has been reported without the usual symptoms.[30] Two fatal cases resulting from protamine zinc insulin have also been reported by these same investigators. Groen and Garrer[31] describe the case of a female diabetic, aged 27 years, unconscious in her 8th month of pregnancy, who died shortly after admission to the hospital with a blood sugar of 20 mg. per 100 cc. She had been on insulin therapy since the age of 15 years. Previous to her admission to the hospital she had been on 12 units of ordinary insulin and 52 units of protamine. In spite of negative urine for sugar or so-called "adequate" control, she was subject to frequent insulin reactions. Just before her admission she was found in profound insulin shock and was given 20 units more of insulin because of mistaken diagnosis for diabetic coma. These authors consider doses of protamine zinc insulin exceeding 40 units too large. "As far as the authors were able to ascertain this was the eighth case in which protamine zinc insulin has been either the main or a contributory cause of death."

Allen's[32] results in his animal studies with protamine zinc insulin, although exaggerated in degree, were similar to those in man: "Loss of appetite, and also the death of rats, rabbits and cats with high doses, seem to show a greater toxicity of protamine than of regular insulin. Delayed action of subcutaneously injected protamine insulin is due to retention at the site of injection, for periods tested up to 62 hours." Allen[33] attributes the fatal results in his group of rats to the cumulative and toxic effects of protamine insulin. However, when the rats were given equal doses of regular insulin because of extreme high tolerance, the effects were trivial in degree and duration. Allen claims that a subcutaneous injection of 10 or 15 units of protamine zinc insulin in a rat produces effects lasting 3 or more days longer than the effects of 500 or 1000 units of regular insulin. He points out that a strong rat can survive 500 or 1000 units of regular insulin whereas 50 or 60 units of protamine zinc insulin is inevitably fatal.

CIRCUMVENTING PROTAMINE ZINC INSULIN REACTIONS

Since the introduction of protamine zinc insulin many attempts have been made to offset the possibility of its hypoglycemic reactions. First, by changing the diet habits of patients. The most common method has been to rearrange or divide the carbohydrate content of the day's allowance so as to meet more nearly the maximum rate of absorption and effect of the protamine zinc insulin.[34, 35] Others advise extra carbohydrate allowance when anticipating exercise.[36] Second, by maintaining glycosuria and hyperglycemia. Many physicians, realizing the danger of protamine zinc insulin hypoglycemia when urine is "sugar free," or the impossibility of avoiding hypoglycemia with maintenance of physiologic levels of the blood sugar,[37] allow a variable degree of glycosuria to exist.[38, 39, 40] Other physicians advise a lower carbohydrate allowance to keep the patients' aglycosuria;[40] others disregard the long established fundamentals of diabetic therapy and allow glycosuria and hyperglycemia, providing the patient maintains weight, freedom from all diabetic symptoms, absence of ketone bodies in the urine, as protection against protamine zinc insulin hypoglycemia reaction[41]. Third, by changing the time of insulin injection. Many physicians advocate the injection of insulin 60 to 90 minutes before meals in an attempt to obtain the maximum effect when the largest portion of carbohydrate allowance of the meal is absorbed,[42] whereas Mark[43] disregards this procedure and advocates protamine any time of day without its relation to meal time as long as it is given at the same interval. Fourth, by discontinuing protamine zinc insulin when reactions are unavoidable, as during summer months when a combination of hard exercise and sunshine occurs,[26] in uncooperative patients,[34] patients with loss of appetite, or those who do not desire to eat, in severe or complicated cases, allergic cases, patients with marked local or systemic reactions,[44] or in coma patients. Fifth, by avoiding unusual exercise.

The sixth method of attempting to control the blood sugar level and eliminating possible hypoglycemia reactions is by mixing protamine zinc insulin with regular insulin. When protamine insulin was introduced in diabetic therapy we realized its marked limitations, especially its inability to control post-prandial hyperglycemia, as well as the danger it presented of protamine zinc insulin hypoglycemia.[1] Lawrence,[45] realizing the failure of the protamine zinc insulin used alone to release sufficiently rapid insulin to control post-prandial hyperglycemia, expressed the opinion that both insulins (ordinary and protamine zinc insulin) be combined in the same syringe and injected together, the regular insulin controlling the post-prandial hyperglycemia, and the protamine zinc insulin with its prolonged action meeting the basal insulin requirements. This thought is still shared by many today.

However, Wauchope's[46] observations revealed relatively more regular insulin was necessary to produce a rapid effect when both insulins were mixed than when it was given separatively. It was evident that the type of action obtained depended upon the relative proportions of regular insulin and protamine zinc insulin, the degree of mixing, and other factors. He suggested that the two insulins be "layered" in the syringe without mixing so as to obtain the separate action of each insulin. However, after injection, mixing is bound to occur and considerable variation might occur in the degree of mixing in the tissues, with consequent effects. This method, stratifying or layering the two insulins, is still advocated by a few clinicians, although not recommended by most advocates of insulin mixtures.

Ulrich[46] emphasized the difficulties encountered in these procedures by recognizing that ordinary protamine zinc insulin contains an "excess" of protamine and that added insulin will combine with the excess protamine and merely make more protamine zinc insulin until an excess of regular insulin is added. He suggested that a mixture containing three parts regular insulin and two parts protamine zinc insulin would be most useful in controlling post-prandial hyperglycemia. Colwell and his associates[47] in their studies with the various mixtures revealed that as the proportion of regular insulin to protamine zinc insulin increased there resulted increased rapidity and intensity of action but decreased

prolongation of effect. In subsequent papers Colwell[4, 5] reported the best results with a 2:1 mixture (2 parts regular insulin and one part protamine zinc insulin). He believes that this mixture is much more generally applicable than protamine zinc insulin alone, and that it will adequately control most diabetics and should replace present commercial protamine zinc insulin. In his conclusion he believes that with the present commercial "Protamine zinc insulin, as now manufactured...too often it is necessary to supplement its action by separate injection or admixture with ordinary insulin...Leads to confusion...Use of this type of insulin as now prepared should be abandoned."

Peck [6] states that protamine zinc insulin contains 1.25 mgm. protamine per 100 units of insulin, which is about twice the amount of protamine theoretically necessary to precipitate this amount of insulin. The excess protamine is used to stabilize the preparation and assure complete precipitation of all the insulin. Therefore, if less than one part of regular insulin is added to one part protomine zinc insulin, there will be very little change in activity since the excess protamine will combine with most of the added insulin, thus making more protamine zinc insulin. As the ratio of regular insulin to protamine zinc insulin is increased over 1:1 (e. g. 2:1, 3:2, 3:1, etc.) the excess insulin will provide greater rapidity of effect and corresponding shorter duration of action.

Peck[7] has published a detailed table showing approximate theoretical amounts of quick-acting regular insulin and prolonged-acting protamine zinc insulin which will be available after mixing various proportions of these two insulins. He has recommended adjusting the mixture to suit the needs of each individual patient. Mixtures used in this manner have been termed "tailor-made" or "extemporaneous" mixtures.

MacBryde et al[2, 3] have conducted investigations with a modification of protamine zinc insulin consisting of one part regular insulin and one part protamine zinc insulin buffered to pH 7.2, as is ordinary protamine zinc insulin. In this respect it differs from the extemporaneous mixtures which have a pH more acid than protamine zinc insulin, the exact pH depending upon the amount of regular insulin added. MacBryde originally called his mixture 3;1 insulin because he believed the final product provided three parts protamine zinc insulin action and one part regular insulin action. This terminology was confusing because the term "3;1" more commonly refers to a mixture made by adding three parts insulin to one part protamine zinc insulin. MacBryde now regards his preparation not as a mixture but rather as a new modification of protamine zinc insulin, differing from ordinary protamine zinc insulin only in that it contains half as much zinc and half as much protamine in relation to a given amount of insulin as does commercial protamine zinc insulin. It cannot be made merely by mixing regular insulin and protamine zinc insulin since it must be buffered to pH 7.2. MacBryde now calls this preparation modified protamine zinc insulin or MPZ.

MacBryde disagrees with Peck's view that insulin mixtures need to be "tailor-made" to suit the individual patient. MacBryde believes that his MPZ will satisfactorily control about 90 per cent of all diabetics. He, therefore, feels that MPZ should replace the present marketed protamine zinc insulin and that the use of extemporaneous mixtures is unnecessary and confusing. He further states that the 2:1 mixture, which Colwell believes to be most satisfactory, does not give regular or consistent results and that its action is not as well suited to most diabetics needs as MPZ.

Colwell[4] has recently published an extensive study of the chemistry and clinical application of mixtures. He has demonstrated that the protamine of protamine zinc insulin is not saturated with insulin when one part of regular insulin is added to one part of protamine zinc insulin, as suggested by the earlier work. His studies indicate that the protamine zinc insulin can combine with two and one-half to three times as much insulin as is present in the commercial product. The modified action of these mixtures is, therefore not due to excess free insulin in solution, as postulated by Peck, but rather to the formation of protamine zinc insulin combination which, because of the increased proportion of insulin in the precipitate, release in-

sulin more rapidly than combinations containing less insulin, (or more protamine).

Colwell[49] has shown that many variables affect the composition and nature of mixtures. On the basis of Colwell's work, MacBryde's contention that his MPZ consists of one part free insulin in solution and three parts precipitated protamine zinc insulin seems open to question. Colwell comments as follows on this matter: "The modification used and described by MacBryde is...judged to be a mixture of rapid-acting insulin in solution and protamine zinc insulin in suspension. As the following experiments show, this may be true under given conditions of mixing, but there are many variables including amount of excess insulin, pH, time of contact before buffering, temperature, amount of zinc present and probably stability of proportions even after buffering...

"There is also good reason to believe that even buffered mixtures which do contain insulin in solution originally may lose it by precipitation on standing in the cold a long time.

"These estimates of supernatant soluble insulin demonstrate the futility of planning modifications containing fixed amounts of insulin in solution. Unless exacting conditions of mixing and buffering are carried out, the component of soluble insulin in any mixture, and thus its action, may be variable."

Globin Insulin

The writer's experimental studies, as well as the therapeutic application of globin insulin with zinc, and his experience with protamine zinc insulin since its inception in diabetic therapy have given him ample opportunity to compare both insulins.

My results with globin insulin as based upon diabetics suffering from various complications, have been most encouraging and satisfactory. The youngest patient is a female, aged 28 months who recovered from diabetic acidosis with plain and globin insulin. At present she is on 14 units of globin insulin twice daily and apparently progressing well. The oldest patient is 85 years old, on 14 units of globin insulin. I have employed globin insulin alone as a single or two separate daily injections in 82% of the cases, or in conjunction with plain insulin in 18% of the cases in patients with various complications, both medical and surgical, as well as pregnancies. In one case of pregnancy the mother was delivered normally of twins, both the mother and children doing well.

The diet habits in the globin insulin patients were not altered or rearranged as is the general custom with the slow acting insulins. The patients were all upon the higher carbohydrate diet, 140-240 gms. per day, the distribution adjusted to the patient's desire usually into 3 equal meals, with the general accustomed late evening meal, such as a glass of milk with 3 soda crackers, sandwich or some other form of carbohydrate allowance. If the patient's occupation permitted, the same amount of carbohydrate allowance as given in the evening was permitted at 3 P. M.

Difference Between the Two Insulins in Solubility and Release of Insulin

Hypoglycemia reaction with globin insulin, although rarely asymptomatic, were less frequent and severe as compared with the protamine zinc insulin. Cumulative effects with globin insulin were not encountered because of the shorter duration of the effect of globin insulin, generally 20 hours, as compared to 27½ hours or more of protamine zinc insulin.

The explanation for the varying rate and degrees of release and absorption of insulin from various insulin combinations resulting in late acute protamine insulin-coma, or latent or delayed insulin reactions as a result of "cumulative" effects, may be explained thus: protamine is a general protein precipitant, whereas globin is not. Hagedorn[54] showed that the solubility of various protamine insulin combinations depended on the amount of serum present. He also recognized the fact that protamine combined with tissue proteins, and suggested that the absorption of insulin could be varied by varying the amount of protamine. Of course variation in the amount of protein in the tissue fluid would likewise modify the solubility and presumably the rate of absorption of insulin from protamine zinc insulin.

Apparently protamine zinc insulin releases insulin primarily by interaction with other proteins, such as tissue fluid proteins. In other words, tissue fluid protein may displace the insulin. A high concentration of tissue

fluid protein, or a small proportion of protamine, would favor the release or solubility of insulin, while a low concentration of tissue fluid protein, or a large excess of protamine, would result in a slight and slow solubility and absorption of insulin.

Globin fundamentally differs from protamine in that it is not a general protein precipitant.[55] It seems that insulin is released from globin insulin by simple solution and dissociation; the solubility varies with the pH, being least at about pH 6. At body pH 7.2 globin insulin has considerable solubility, which would account for its relatively rapid release of insulin.

These chemical differences between globin insulin with zinc and protamine zinc insulin is substantiated by the work of Reiner and his associates.[56] They have shown a correlation between the rate of insulin absorption from the site of injection and the intensity of hypoglycemic effect with insulin labelled with radioactive iodine. A rapid decrease in radio-activity was usually associated with low blood sugars. Thus it required 15 times longer for protamine zinc insulin, and about 3 times longer for globin insulin, than for ordinary insulin to reach the level at which 40% of the radio-activity had disappeared. At this point it was found that the protamine zinc insulin curve appeared to be starting to level off, occurring about 12 hours following the injection, whereas the globin insulin curve tends to flatten out after about 65% of the radio-activity had disappeared.

Our higher carbohydrate diets ranging from 140-240 gms. per day, arranged in a manner best suited for the patient instead of meeting the so-called maximum period of absorption of the slow-acting insulins, as has been the general custom, approaches the normal diet as near as possible. Our observations in the past have revealed that 80% of the patients coming to our metabolic clinics after they were given careful diet instructions disregarded them.[57] This finding was also common in the private patients. It is a significant observation for those physicians who insist upon denying their patients food they most desire or who advocate low carbohydrate diets or those physicians who change the diet habits or customs of patients.

CONCLUSION

The writer's observations, as well as other investigators, have revealed that protamine zinc insulin hypoglycemia reactions are not without danger especially upon the cardio-vascular; the neurological, and the endocrine systems. Not infrequently these reactions have precipitated fatal results.

Cognizant of the frequency and seriousness of protamine zinc insulin hypoglycemia, physicians have attempted to circumvent them.

The use of protamine and plain insulin mixtures is an uncertain solution and no particular mixture thus far has been generally accepted as satisfactory.

Protamine zinc insulin therapy undertaken by an inexperienced physician may invite serious consequences.

Globin insulin with zinc therapy was found by the author to be preferable to protamine zinc insulin therapy.

Of 786 patients under our care, 82% are being adequately controlled with a single or double daily injection of globin insulin alone, and 18% when it is given with plain insulin.

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BIBLIOGRAPHY

1. Sindoni, A. Jr.: Protamine Insulin versus Ordinary Insulin, J. A. M. A. **108**: 1520-27 (April 17) 1937.
2. Editor: Danger of Protamine Insulin, J. A. M. A. **111**: 254 (July 16) 1938.
3. Editor: Hypoglycemia from Protamine Insulin, Brit. Med. J. No. 4260, 250, 1942.
4. Klein, F. and Ligsterink, J. A.: Insulin and Cerebral Damage, Arch. Int. Med. **65**: 1085-1096, June, 1940.
5. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, J. A. M. A. **110**: 92-96 (Jan. 8) 1938.
6. Sherrill, J. W. and MacKay, E. M.: Deleterious Effects of Experimental Protamine Insulin Shock, Arch. Int. Med. **64**: 907-912 (Nov.) 1939.
7. Gellhorn, E.: The Action of Hypoglycemia on the Central Nervous System, J. A. M. A. **110**: 1433-1434 (April 30) 1938.
8. Himwich, H. E.; Bowman, K. M.: Wortis, J. and Fazekas, J. F.: Metabolism of the Brain During Insulin and Metrazol Treatments of Schizophrenia, J. A. M. A. **112**: 1572-1573 (April 22) 1939.
9. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**: 1098-1100 (Dec.) 1937.
10. Allen, F. N. and Crommelin, R. M.: Cerebral Damage from Insulin Shock, J. A. M. A. **118**: 373-374 (Jan. 31) 1942.
11. Reese, H. H. and Vander Veer, A.: Protamine Zinc Insulin: Its Unsuitability for Hypoglycemia Shock Therapy, Arch. Neur. & Psych. **39**: 232 (Feb.) 1938.
12. Himwich, H. C. and Fazekas, J. F.: The Effect of Hypoglycemia on the Metabolism of the Brain, Endocrin, **21**: 800-807 (Nov.) 1937.
13. Malamud, N. and Grosh, L. C. Jr.: Hyperinsulinism and Cerebral Changes, Arch. Int. Med. **61**: 579-599 (April) 1938.
14. Baker, A. B. and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **29**: 190, 1937.
15. Berman, L. and Riess, B.: The Effect of Insulin Shock on Learning in the White Rat, Science, **95**: 511-512, No. 2472 (May 15) 1942.
16. Drysdale, H. R.: Protamine Insulin in Juvenile Diabetes, J. A. M. A. **103**: 1250-1257 (April 10) 1939.
17. Wilder, R. M. and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **54**: 329-364 (Feb.) 1937.
18. Soskin, S.; Katz, L. M.; Strouse, S. and Rubinfield, S. H.: Treatment of Elderly Diabetic Patients With

Cardio-Vascular Disease, Arch. Int. Med. 51: 123-142 (Jan.) 1933.
19. Blake, K. W.: Transitory Hyperglycemia and Glycosuria in Acute Coronary Occlusion, J. A. M. A. 108: 443-445 (Feb. 6) 1937.
20. Gignon, A.: Diabetes, Insulintherapie, Schweiz, Med. Wchnschr. 53: 882-887 (Sept. 20) 1923.
21. Himwich, H. E.: Goldforb, W. and Fazekas, J. F.: The Carbohydrate Metabolism of the Heart During Pancreas Diabetes, Amer. Jour. Phys. 114: 273 (Jan.) 1936.
22. Goldman, D.: The Electrocardiogram in Insulin Shock, Arch. Int. Med. 66: 93-108 (July) 1940.
23. Sherrill, J. W.: Clinical Experience and Experiments with Protamine Zinc Insulin: The Potential Danger of Hypoglycemia, Calif. and West. Med. 14: 13 (July) 1938.
24. Walther, G. and Ammon, R.: Anaphylactic Shock After Protamine, Klin. Wochensch. 18: 288 (Feb. 25) 1939.
25. Mirsky, I. Arthur; Nelson, Norton; Elgart, S. and Grayman, Isabelle: The Production of Permanent Hyperglycemia and Glycosuria by the Prolonged Administration of Insulin, Science 95: 583, No. 2475, 1942.
26. Best, C. H. and Haist, R. E.: The Effect of Insulin Administration on the Insulin Content of the Pancreas, Jour. Phys. 100: 142, 1941.
27. Rosenbaum, J. D.: DeKruif, H. and Lavietes, P. H.: The Effect of Insulin on the Glucose Tolerance of Normal Man, Jour. Clin. Invest. 23: 45-49 (Jan.) 1944.
28. Margolin, M.: Protamine Insulin in Treatment, with Reports of Fatal Case of Hypoglycemia, Nebr. Med. J. 23: 92-97, 1938.
29. Margolis, H. M. and Eisenstein, V. W.: Treatment of Diabetes Mellitus with Four-meal Diet Means of Circumventing Certain Difficulties Arising in Use of Protamine Zinc Insulin, Ann. Int. Med. 14: 67-87, 1940.
30. Boller, R. and Pilgerstorfu, W.: Die Hypoglykamie bei Protamine Zinc—Insulinanwendung, Klin. Woch. 17: 31, 1065-1068, 1938.
31. Groen, J. and Garrer, A. H.: Death by Hypoglycemia During with Protamine Zinc Insulin, Nederlandsch Tydschrift V. Geneeskunde 83: 1844 (April 22) 1939. Abst. J. A. M. A. 113: No. 6, 548, 1939.
32. Allen, F. M.: Tolerance and Toxicity of Insulin. III Protamine and Zinc Compounds, Ann. Int. Med. 12: 1870 (May) 1939.
33. Allen, F. M.: Spontaneous and Artificial Hyperinsulinism, Jour. Clinic. Endocrin. 1: 595-603 (July) 1941.
34. Smith, Leslie B.: Diabetes Mellitus with Analysis of Cases Treated with Protamine Zinc Insulin, Southwest. Med. 23: 288 (Sept.) 1939.
35. Martin, Helen; Drury, D. P. and Strouse, S.: Basal Insulin Requirement in Diabetes Mellitus, Arch. Int. Med. 66: 78-92 (July) 1940.
36. Mosenthal, H. O. and Mark, M. F.: The Prolonged Use of Protamine Zinc Insulin, J. A. M. A. 113: 17-22 (July 1) 1939.
37. Boyd, J. D. and Jackson, L. R.: Levels of Control in the Treatment of Diabetes Mellitus, J. A. M. A. 111: 906-909 (Sept. 3) 1938.
38. Gang, Lawrence, B.: New Criteria in the Treatment of Diabetes Mellitus with Protamine Zinc Insulin, West. Virg. Med. J. 37: 214 (May) 1941.
39. Lande, H.: Present Status of Protamine Insulin, Bull, N. Y. Acad. Med. (2), 15: No. 4, 273-281, 1929.
40. Lawrence, R. D.: Zinc Protamine Insulin in Diabetes Treatment by one Daily Injection, Brit. Med. J. 1: 1077 (May 27) 1939.
41. Tolstoi, E.: Newer Concepts in the Treatment of Diabetes Mellitus with Protamine Insulin, Amer. Jour. Digest Dis. and Nutr., 10: 247-253 (July) 1943.
42. Root, H. F.; White, Priscilla; Marble, Alexander and Stotz, E. H.: Clinical Experience with Protamine Insulinate, J. A. M. A. 106: 180 (Jan. 18) 1936.
43. Mark, Morton F.: Optimum Time For Administration of Protamine Zinc Insulin, Arch. Int. Med. 64: 897-906 (Nov.) 1939.
44. Robson, G. B. and Gray, H.: Protamine Insulin, Three Practical Points, Endocrin 23: 800-802 (Dec.) 1938.
45. Wauchope, G. M.: Zinc Protamine Insulin and Soluble Insulin Interaction in Combined Doses, Lancet 1: 963, 1940.
46. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulin, Ann. Int. Med. 14: 1166, 1941.
47. Colwell, A. R.; Izzo, J. L. and Stryker, W. A.: Intermediate Action of Mixture of Soluble Insulin and Protamine Zinc Insulin, Arch. Int. Med. 69: 931, 1942.
48. Colwell, A. R. and Izzo, J. I.: Protamine Zinc Insulin Modified for Accelerated Action, J. A. M. A., 122: 1231, 1943.
49. Colwell, A. R.: Nature and Time Action of Modification of Protamine Zinc Insulin, Arch. Int. Med. 74: 331, 1944.
50. Peck, F. B.: Action of Insulins, Proc. Amer. Diabetes Assoc. 2: 69, 1942. Treatment of Uncomplicated Diabetes with Mixtures of Insulin and Protamine Zinc Insulin, J. Indiana M. A. 36: 340-348, 1943.
51. Peck, F. B.: Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin, Ann. Int. Med. 18: 177, 1943.
52. MacBryde, C. M. and Roberts, H. K.: "Three to One:" Modified Protamine Zinc Insulin. An Improvement on Market Protamine Zinc Insulin. Proc. Centr. Soc. Clinic Research 15: 7, 1942; J. A. M. A. 121: 1243, 1943. A New Modified Protamine Zinc Insulin. J. Clin. Invest. 22: 791, 1943. Modified Protamine Zinc Insulin, An Improvement on Standard Protamine Zinc Insulin. J. A. M. A. 122: 1225, 1943.
53. MacBryde, C. M. and Reiss, R. S.: Modified Protamine Zinc Insulin: Comparison with Globin Zinc Insulin and Insulin Mixtures, J. Clin. Endocrin. 4: 469, 1944.
54. Hagedorn, H. C.; Jensen, B.; Krarup, N. B. and Wodstrup, I.: Protamine Insulinate, J. A. M. A. 106: 177 (Jan. 18) 1936.
55. Reiner, L.; Searle, D. S. and Lang, E. H.: On the Hypoglycemic Activity of Globin Insulin. Jour. Pharm. & Exper. Therap., 67: 330-340 (Nov.) 1939.
56. Reiner, L.; Lang, E. H.: Irvine, J. W. Jr.; Peacock, W. and Evans, R. D.: The Absorption Rates of Insulins, Globin Insulin and Protamine Zinc Insulin Labelled with Radioactive Iodine, Jour. Pharm. & Exper. Therap., 78: 352-357, 1943.
57. To be published.

CLINICAL CASES FROM THE HOSPITALS

MALIGNANT NEUTROPENIA

Case Report With Recovery

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INTRODUCTION

In 1902 Brown described a disease characterized by a marked decrease of white blood cells which have their origin in the bone marrow[1]. Twenty years later this disease received its first name—agranulocytosis[2]. Since then, more than a dozen different names were suggested, most of them with the ominous adjective "malignant". Truly, up to recent days, the mortality rate of this disease was 70 to 90 per cent of the morbidity. However, modern organo- and chemotherapy, which has already obliviated the pernicious or malignant character of many a disease, will shortly cope with granulocytopenia as well.

Idiopathic chronic neutropenia seems to be quite frequent, while acute fulminant neutropenia is not common[3]. However, the acute forms are readily diagnosed and thus appear more numerous than the asymptomatic chronic states[4].

The clinical signs and symptoms of the acute disease are upper respiratory infection, generalized pains, hyperpyrexia and chills, headache, nausea and prostration. Edema of the mucous membranes of the air passages leads to dyspnoea and cyanosis. The onset

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is sudden, usually with a sore throat; the development of the full clinical picture is a rapid one. A complete hematologic examination allows its differentiation from the leukopenia of influenza, from aleukemic leukemia, from infectious mononucleosis, and from aplastic anemia. On first examination the typical blood picture consists of a white blood cell count below 1,000 per cu.mm., of which 90 per cent are lymphocytes and 10 per cent are monocytes[5]. The diagnosis can be confirmed by bone marrow studies.

The bone marrow is either of a hyperplastic type with an abundance of stem cells—myeloblasts, or of a hypoplastic or almost aplastic type which is practically void of myeloid elements, occasionally there is an abundance of reticulo-endothelial elements, and, rarely, the marrow is normal. The hyperplastic type is mostly seen in persons who succumb to the disease within a few days; the hypoplastic marrow in patients who die after prolonged illness. During improvement there is a progressive maturation of the hematopoietic tissue characterized by the appearance of myelocytes and young leukocytes[5]. Beside the myelogram, the microscopic structure of the lesions of the pharynx and lungs are typical: there is necrosis, exudation of fluid and of fibrin, of a few lymphocytes and monocytes; leukocytes are conspicuously absent.

There is a variety of chemical, physical or bacteriologic causes of acute granulocytopenia. The most common agents are amidopyrine[7,8], acetphenetidin, phenacetin, empirin compounds, acetanilid, pyramidon[9,10], dinitrophenol, arsphenamine[10,11], and other benzene derivatives[12], then barbiturates[7,10], gold salts[10] and thiouracil[13]. In one instance a few small doses of a drug will produce neutropenia; in other patients granulocytopenia appears suddenly, a long time after large doses of the same drug have been given. None of the chemicals or microorganisms produce neutropenia regularly, and it is obvious that another factor must be involved in the genesis of this disease.

The search for such a factor created many theories. Some authors suggested idiosyncrasy, others sensitization. The stem cell hyperplasia is held proof of a maturation arrest[14]. It is reasoned that there is lack of a nutritional factor[15] which lately is believed to be identical with pyridoxin-vitamin B_6[16].

Up to now, the treatment of acute neutropenia consists of nucleoproteids in the form of pentnucleotides[17], yellow bone marrow, ascorbic acid, vitamin complex, vitamin B_6[16], liver extract, iron, and blood transfusions.

In spite of intensive treatment the mortality of the acutely ill remains high. Although it is still disputable as to whether neutropenia accompanies an acute infection or whether the two conditions are concurrent, the fact remains that the patients die either of septicemia or of broncho-pneumonia. The stoppage of the spread of an existing infection and the prevention of secondary infections should be the goal of our treatment. It should, if our conception proves right, reduce future fatalities from granulocytopenia.

CASE REPORT

A 57 year old, normally developed and nourished, colored man was admitted to the Wilmington General Hospital (service Dr. Sidney Chavin) in a semi-comatose state with a generalized maculo-papular rash, areas of purpura over the entire body, and a hyperpyrexia of 104°.

The family and personal history were essentially negative. Approximately six months before hospitalization the serologic tests for syphilis, performed by the State Laboratory, were positive. The patient had received 10 intravenous injections of 60 mg. doses, or a total of 0.6 gm of arsphenamine.

Four days prior to admission the patient developed high fever, a generalized macular rash, bled from the nose, and vomited. On admission, the patient appeared acutely ill; upon physical examination, however, nothing was seen but signs of multiple generalized hemorrhages.

Laboratory studies revealed repeatedly positive tests for albumin in the urine, red and white blood corpuscles, and coarse granular casts in the urine sediment, and a positive test for occult blood in a stool sample. The blood sugar level equaled 98 mg. per 100 ml., the blood urea nitrogen 15.4 mg. per 100 ml. Agglutination tests for enteric diseases were negative. The seroreactions for syphilis

were negative on admission (6-26-45) and again during the patient's stay at the hospital (7-17-45); before his discharge (8-8-45), the Kahn test was negative while the Wassermann reaction turned positive.

The appearance of blood elements in the urine and in the feces indicated internal purpura. The hematologic findings served as a basis for the correct diagnosis. Because of frequent repetition, the results of blood examinations are presented in the form of charts and a graph. To classify the patient's

Dates 1945	Hb* gm.	Red Cells per cu.mm.	White Cells per cu.mm.	B. %	E. %	St %	N. %	Ly %	Mo %	Platelets per cu.mm.
6- 26	10	3,150,000	870	0	0	0	0	90	10	6,300
27	10	3,830,000	780	0	2	1	3	92	2	
30	7½	2,780,000	570	0	0	2	3	95	0	
7- 2	8	3,190,000	510	0	0	3	2	95	0	
5	8	3,330,000	1,500	0	0	7	18	72	3	
8			1,870	0	0	12	24	58	6	
10	8	2,700,000	1,400	0	0	5	23	65	7	
14			4,300	0	0	7	43	45	5	
17	7	2,380,000	6,450	0	2	2	38	50	8	149,900
23	6½	2,310,000	7,250	0	2	2	68	18	10	
25	7	2,530,000								
30	8	2,340,000	10,500	0	5	2	59	31	3	
8- 2	8	2,600,000								
6	9	2,810,000	9,750	4	6	1	51	29	9	
9	9½	3,160,000								
9- 13	12	3,960,000	8,300	2	2	3	64	21	8	

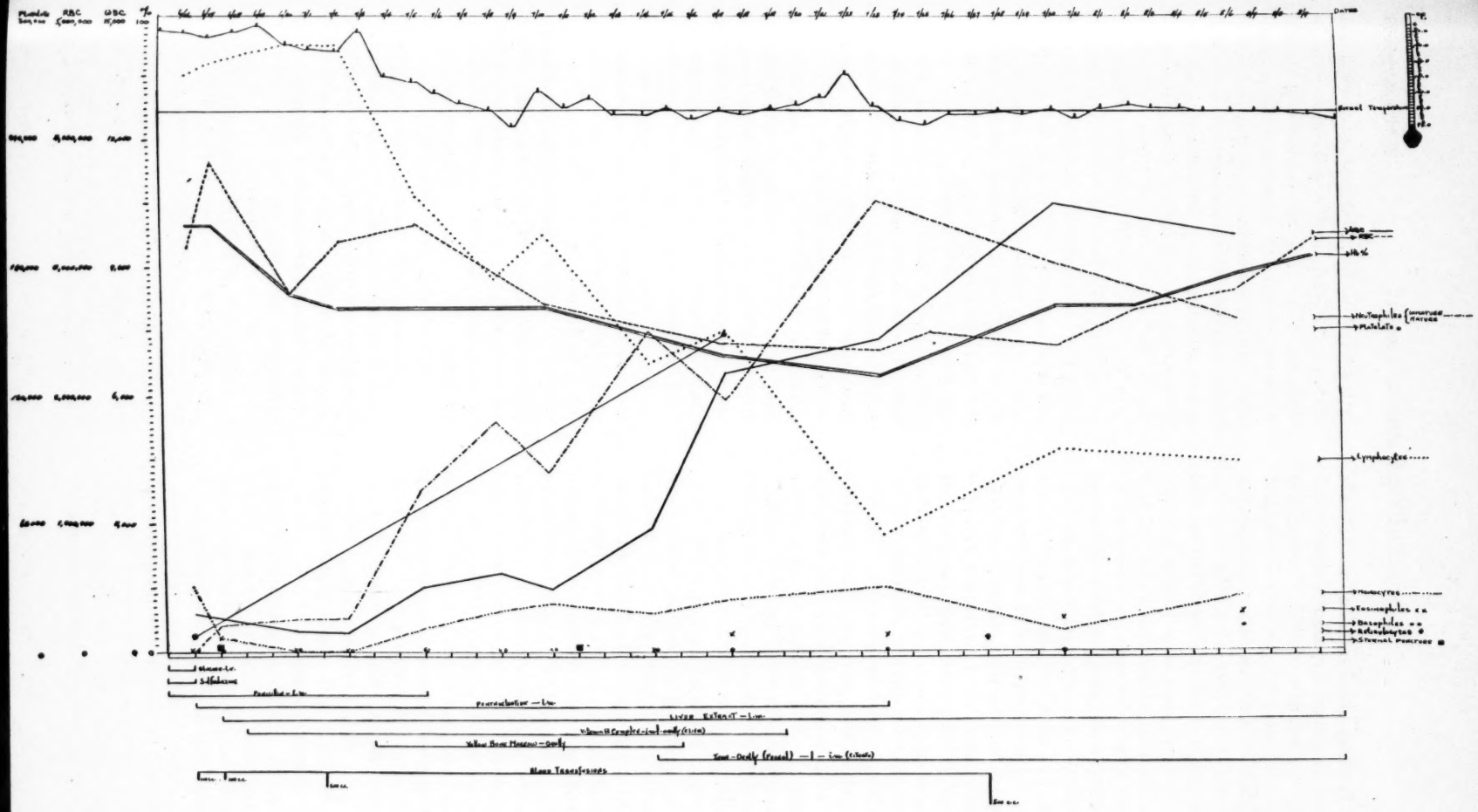
* Hb -hemoglobin, B -basophilic, E -eosinophilic, St -stab cell, N -neutrophilic mature, Ly -lymphocytes, Mo -monocytes.

CHART 1. Peripheric blood findings of a patient with acute neutropenia during hospitalization and a month after discharge.

Dates	6 — 26 — 45			7 — 10 — 45		
Paramyeloblasts	10			0		
Myeloblasts	1			10		
Premyelocytes	1*	14	18	4	28	36
Myelocytes	0			8		
Metamyelocytes	0			2		
Stab cells	2			4		
Polymorphonuclears	4*	4		8	8	
Lymphoblasts	2	68	78	1	47	52
Lymphocytes	66			46		
Plasmatocytoblasts	2			0		
Plasmatocytes	3	8		1	5	
Monocytes	3			4		
Megakaryocytes	1	1		0	0	
Reticulo-endohelial cells	1	1		0	0	
Megaloblasts	3			4		
Erythroblasts	1	4	4	8	12	12
Normoblasts	0			0		
Nucleated cells; total			100			100

* eosinophilic

CHART 2. Myelograms of a patient with acute neutropenia on diagnosis and during recovery.



OUTSTANDING DATA OF BLOOD FINDINGS AND TREATMENT IN A PATIENT WITH ACUTE MALIGNANT GRANULOCYTOPENIA

anemia, further blood studies were made (7-25-45). The mean corpuscular volume was 83 cu.mi., the mean corpuscular hemoglobin 28 gamma, the mean corpuscular hemoglobin concentration 33 per cent, the volume index 0.8, and the color index 0.9. In the fragility test initial hemolysis occurred at 0.44 per cent and complete hemolysis at 0.34 per cent of sodium chloride solution; 1.8 per cent of all red corpuscles were reticulocytes.

The patient's progress is clearly illustrated by the charts of peripheric blood findings (Chart 1) and of myelograms (Chart 2) and especially by the graph which includes temperature records and therapeutic procedures.

Although there was no evidence of upper respiratory infection—in which respect our patient was atypical—large doses of penicillin were injected to prevent infection during the period of severe neutropenia. Pentnucleotides, yellow bone marrow, and vitamin B complex were administered because they represent the standard treatment. Because the patient reacted to repeated transfusions with chills, liver and iron were give to ameliorate his anemia.

The patient's temperature began to drop within one week and reached the first normal value on the tenth day just when the first increase of white blood cells (from 510 to 1500 per cu.mm.) and of granulocytes (from 5 to 25 per cent) was noticed. No more penicillin was given thereafter. A definite turning point occured after three weeks with the white count reaching 4,300 cells per cu.mm. and granulocytes numbering 50 per cent of the white cells; the patient left his bed. The yellow bone marrow, vitamins and pentnucleotids were gradually discontinued. At this point, however, the erythrocyte count had decreased, and the liver treatment of anemia, initiated previous to this date, had to be intensified and fortified by a transfusion.

The patient was discharged after 46 days of hospitalization. Frequent controls revealed a steady improvement under anti-anemic treatment. A month after hospitalization (9-13-45) the blood picture stabilized at about a normal level. Physically, the patient is well.

DISCUSSION

The hyperpyrexia of our patient was caused either by hemorrhage into the thermoregulatory center or by acute nephrities. The fact that it subsided under penicillin therapy indicates that there was a hidden infection. At the same time, the administration of penicillin is held imperative to decrease the mortality rate from septicemia of patients with granulocytopenia. It is believed that this treatment saved our patient's life. Regeneration of the bone marrow will frequently occur with the cessation of exposure to chemicals or of the intake of drugs which precipitated the neutropenia. Pentnucleotids, yellow bone marrow, vitamin complex, and probably even pyridoxine, which is believed to be responsible[18] for maturation and migration of the myelogenous elements, are adjuvants to the process of cell formation.

The question whether or not, in our patient, arsphenamine caused the acute neutropenia could only be answered by renewed medication with the same drug. It would be hazardous to do so and to risk another episode of neutropenia for the sake of scientific proof. It is known that granulocytopenia from arsenicals does not show the well-marked bone marrow proliferation of myeloblasts found in instances of idiopathic agranulocytosis with maturation arrest. There are a number of blood dyscrasias which may follow arsphenamine injections: thrombocytopenia; granulocytopenia, a combination of both; or aplastic anemia. Severe depression of myelopoiesis, marked depression of thrombocytopoiesis and of erythropoiesis as well occur mostly after a larger series of injections of arsenicals—as it was in the case of our patient.

SUMMARY

A patient with acute granulocytopenia, most likely precipitated by arsphenamine, was cured by intensive medication. Penicillin played a major role in the patient's cure. The nature and treatment of malignant neutropenia is discussed.

REFERENCES

1. Brown, P. K.: Am. Med. 3: 649, 1902.
2. Schultz, W.: Dutsche Med. Wchnschr. 48: 1495, 1922.
3. Roberts, S. R., and Kracke, R. R.: Ann. Int. Med. 5: 4, 1931.
4. Moore, R. A.: A Textbook of Pathology: Philadelphia, W. B. Saunders Co., 1944, p. 744.
5. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis; St. Louis, C. V. Mosby Co., 1943, vol 1, p. 578.
6. Darling, R. C., Parker, F. Jr., and Jackson, H. Jr.: Am. J. Path. 12: 1, 1936.
7. Watkins C. H.: Proc. Staff Meet., Mayo Clinic 8: 713, 1933.
8. Von Bonsdorff: Klin. Wchnschr. 14: 449, 1935.

9. Kracke, R. R.: Am. J. Clin. Path. 1: 385, 1931.
10. Kracke, R. R., and Parker, F. P.: J. Lab. & Clin. Med. 19: 779, 1934.
11. Kracke, R. R.: J. A. M. A. 111: 1255, 1938.
12. Madison, F. W., and Squire, T. L.: J. A. M. A. 102: 755, 1934.
13. Wosika, P. H., and Braun, L.: J. Lab. & Clinic. Med 30: 779, 1945.
14. Fitz-Hugh, T., and Krumbhaar, E. B.: Am. J. Med. Sci. 183: 104, 1932.
15. Miller, D. K., and Roads, C. P.: J. Exper. Med. 61: 173, 1935.
16. Cantor, M. M., and Scott, J. W.: Canad. M. A. J. 52: 368, 1945.
17. Ferguson, J. W.: Lancet, 1: 334 (Nov. 3) 1944.

PENICILLIN TREATMENT OF PNEUMOCOCCIC MENINGITIS

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INTRODUCTION

Pneumococcic meningitis is a frequent infection and is often overlooked until convulsions, stupor, marked restlessness, and neck rigidity make their appearance. In infants and young children it often follows pneumonitis or otitis media. Unexplained fever, a bulging fontanel, or nuchal rigidity, which may be difficult to elicit in infants, should always arouse a suspicion and should prompt diagnostic thoracocentesis. A cloudy spinal fluid is evidence enough for the immediate institution of treatment for bacterial meningitis, pending laboratory reports as to the type of micro-organism involved. Good results depend on early therapy.

Numerous single case reports and elaborate statistics established the facts of the beneficial effects of the various sulfonamides and of penicillin on many a disease with a formerly high mortality rate. The presentation of three patients cured of pneumococcic meningitis by the combined use of these drugs would be superfluous should the report not serve as a pretext for a premeditated discussion.

CASE 1

A six-year-old girl was apparently well until February 27, 1944. The next day the child did not feel well, complained of left earache, and showed signs of throat infection. On the morning of the following day she was too sick to get out of bed; at about 11 o'clock she became listless and would not answer questions; in the afternoon she developed rigidity of the neck and nystagmus, her eyes turned upward and she became comatose. The only important point in the history was the fact that the child had a moderately severe attack of catarrhal jaundice with liver enlargement which started on the 10th of January, 1944, and lasted for four weeks.

On admission to the hospital the child had all the classical symptoms of meningitis. The organism responsible for the disease was an atypical Pneumococcus seen in chains of up to twenty members. This micro-organism was cultured from the cerebrospinal fluid and the blood as well. The important laboratory findings were charted together with the temperature curve and the therapy (Chart 1—Patient 1).

The patient's temperature became normal on the fourth day of hospitalization but increased again as soon as the dose of sulfamerizine was reduced. The reduction was warranted by the high blood level of the drug. The tenth day the child's neck was still stiff and the Brudzinski sign positive: the left eardrum was slightly dull, a small patch of urticaria appeared on the left buttocks, and secondary anemia developed. A slight bilateral papilledema suggested partial basilary block caused by fibrinous exudate. During the course of illness sulfamerizine was replaced first by sulfadiazine, on the fifteenth day by sulfapryridine, and on the seventeenth day by sulfathiazole. On the eighteenth day the child's condition became critical, and a request was made for penicillin. Meanwhile, large doses of sulfamerizine were given to the patient. Penicillin was first started on the twentieth day of hospitalization. Next day the temperature began to decrease and remained normal under penicillin therapy. Upon exhaustion of the supply of the drug, the temperature increased again and so did the spinal fluid cell count. A second course of penicillin, which ended on April 4, 1944, resulted in final cure and discharge after forty days of hospitalization.

CASE 2

A six-months-old girl was admitted to the hospital January 1, 1945 because of malaise and fever of seven days duration. The child had a fever, vomited, cried constantly, and

*From the Doris Memorial Hospital, Wilmington.
The penicillin was provided for case number one by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

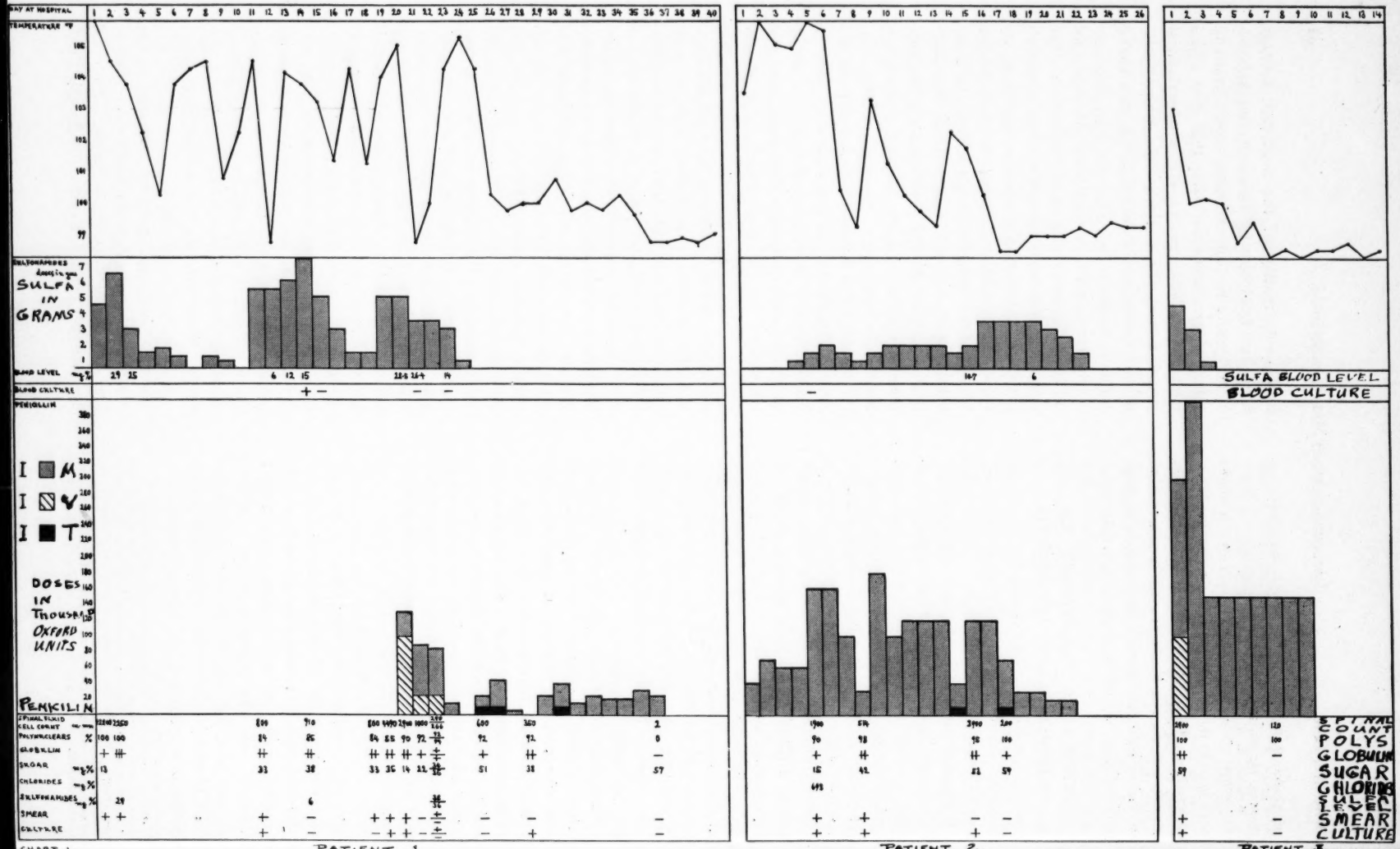
DAY AT HOSPITAL
TEMPERATURE °F
SULFA IN GRAMS
BLOOD LEVEL
BLOOD CULTURE
PENICILLIN
I M
I V
I T
DOSES IN THOUSANDS OF OXFORD UNITS
PENICILLIN
SPINAL FLUID CELL COUNT
POLYMORPHONUCLEARS %
GLOBULIN
SUGAR
CHLORIDES
SULFONAMIDES
SMEAR
CULTURE
SULFA BLOOD LEVEL
BLOOD CULTURE
PATIENT 1
PATIENT 2.
PATIENT 3.

CHART 1.

was restless. She had several generalized tetanic convulsions. The physical examination revealed signs of pneumonitis. A chest x-ray showed increased bronchiovascular markings. There was no evidence of nuchal rigidity or bulging of the anterior fontanel. On the fifth day after admission the anterior fontanel was under increased pressure. The spinal fluid pressure was increased, the fluid itself was cloudy, and a strain of Pneumococcus type XIX was cultured. The blood culture was negative. The laboratory findings the temperature curve, and the therapy were charted (Chart 1—Patient 2).

Penicillin therapy was started on the first day, the treatment with sulfamerizine on the fourth day of hospitalization. Within eight days the child improved to such an extent that the dosage of both drugs was reduced. The next day, however, the child was worse and large doses had to be given for several days. A second drop in temperature occurred on the thirteenth day. Again, discontinuation of intense medication resulted in a relapse. Sulfamerizine was replaced by sulfadiazine. On the seventeenth day the condition improved greatly, and the dose of both drugs was gradually decreased and finally discontinued after twenty-two days. The child was discharged after twenty-six days of hospitalization.

CASE 3

A six-year-old boy was taken to the hospital on November 21, 1945, after a week's illness which began with headeache, earache, fever, and generalized malaise. The child had been treated for an upper respiratory infection, and was apparently improving. The day before hospitalization, however, the boy complained of pain in the neck and severe pain on any attempt at flexion. On admission the child had a temperature of 102.6° and was apparently ill. He complained of headache and neck pain and held his head in extension. There were signs of upper respiratory infection. Otherwise, the physical examination was negative, the reflexes were normal, and there was no evidence of muscle spasm. The spinal fluid pressure was moderate, the fluid was cloudy the cell count high, and the culture revealed a Pneumococcus type III. Again, spinal fluid findings, temperature, and therapy were charted (Chart 1—Patient 3).

Penicillin and sulfadiazine were administered from the first day on. The child's temperature dropped to normal within twenty-four hours and remained normal thereafter. The neck rigidity improved within forty-eight hours so that the child was able to flex his neck forward moderately without any pain. Within seven days he was able to sit up, bend forward freely, and felt very well. At this date the spinal fluid findings showed marked tendency to the normal state. The sulfamerizine treatment was discontinued after three days and the penicillin therapy after nine days. After fourteen days the child was discharged from the hospital. His general condition on January 7, 1946, was normal in every respect.

ANALYSIS OF TREATMENT

The fortunes of the pneumococcic meningitis patient began to improve with the development of chemotherapy. 100% mortality was considerably reduced by the sulfa drugs and by specific antiserum.[1] More substantial improvement was made, however, by the use of penicillin alone, and more so by the combined use of sulfonamides and penicillin.[3] In 1943, Hodes[3] and associates reported their results with sixty patients with pneumococcic meningitis treated with sulfa drugs. The rate of recovery as a whole was 42%; for those over two years of age being 64%, while for those under two years of age it was 22%. The higher mortality was due to delay in instituting treatment. In a review of the literature Hogg and Bradley[4] reported that of twenty-eight instances of pneumococcic meningitis occurring in the first two weeks of life, death occurred in 26 of the infants. The diognosis was made by lumbar puncture in 11 (40%) of the patients during life, and the diagnosis of the remaining seventeen (60%) was made post mortem.

Recurrences in pneumococcic meningitis have been reported when the patients were treated with sulfonamides alone or combined with specific rabbit antiserum. Penicillin has lessened the possibility of recurrence.

Several types of sulfonamides were given to the first child, hoping to obtain a more satisfactory response. The chart indicates the

high blood levels obtained. Penicillin was given intravenously (150,000 Oxford units), intramuscularly (420,000 units), and intrathecally (30,000 units). Intravenously, the drug was given in 100,000 units in 500 cc. of physiologic saline at the rate of 100 cc. per hour. Three doses of 10,000 units each were given intrathecally (on March 24, 25, and 26). The intramuscular doses were of 5,000 and 10,000 units each. Iron, thiamine chloride, and ascorbic acid were therapeutic adjuvants. Two blood transfusions of 200 cc. each were given (on March 14 and 21). Intravenous glucose was administered on occasions.

The second child was treated with sulfamerizine, sulfadiazine and penicillin This was given intramuscularly, intraspinally, and intracisternally in doses up to 180,000 units a day. The supportive treatment consisted of parenteral administration of fluids, of 5 per cent glucose, and in blood transfusions through the bone marrow.

The third patient received sulfamerizine, sulfadiazine, and penicillin. The total amount of penicillin given during the disease was 1,750,000 units. It was administered intravenously the first day (100,000 units) and intramuscularly for nine days in doses up to 400,000 units per day. No penicillin was given intrathecally

DISCUSSION

The chief reason for reporting these cases is to emphasize the observation that intrathecal or intracisternal use of penicillin should not be the rule but the exception if at all necessary, in the treatment of pneumococcic meningitis. In the treatment of meningococcic meningitis and of poliomyelitis we have made it a practice to follow the teachings of Hoyne[8] who has insisted for years that intrathecal therapy and multiple spinal punctures are not necessary and in many cases harmful to the patient. Indeed, symptoms of meningitis constitute only a small part of the picture of a violent generalized systemic infection the patient is suffering from, and any attempt to treat the spinal canal locally will surely fail to eradicate the disease. The use of sulfonamides intrathecally, when first introduced, had very unfavorable results.

At the present our practice is characterized by the effort to make the diagnosis clinically. If this cannot be accomplished, a spinal puncture is performed under strict aseptic precautions. In meningococcic meningitis, intrathecal therapy of any kind is never given and a second spinal puncture is not performed. In poliomyelitis a spinal puncture is not done at all if the diagnosis can be established clinically, because spinal punctures have produced unfavorable sequelae and a negative report of the spinal fluid does not exclude poliomyelitis.

In pneumococcic meningitis many authors have been strongly in favor of intrathecal and intracisternal administration of penicillin.[4] We have objected to this form of therapy (see discussion of [4] p. 41) because of its possibility of producing meningeal irritation, secondary infections, and many other complications[7, 8]. Dangerous complications have already been reported.

The ill effects of the intrathecal therapy, which obviously necessitated one or two lumbar punctures daily for seven or more days, were cellulitis, meningitis due to reinfection through the lumbar puncture, blockage of the cranial foramina with resulting hydrocephalus, headache, nausea, and a case of optic atrophy with total blindness in a two-month-old infant following a single injection of 20,000 units of penicillin intrathecally. The author states that this occurrence may bear no relationship to the intrathecal dose of penicillin, but it should give us pause before injecting unnecessarily large amounts of penicillin into the spinal canal.

During the treatment of the first of our patients, the following experiment was made on March 21, 1944: a spinal tap was done and the needle left in situ while 25,000 units of penicillin were injected intravenously. Thirty-five minutes later a second specimen of cerebrospinal fluid was removed. Both specimens of fluid were assayed for penicillin by Dr. James Kakavas, bacteriologist at the University of Delaware. The first sample did not contain any trace of penicillin and gave a culture of Diplococcus pneumoniae, while the second sample contained one-tenth unit of penicillin per cc. and was free of bacteria.

A single experiment of this nature does not

allow definite conclusions. It stimulates, however, speculation as to the merits and demerits of intravenous and intrathecal penicillin therapy in patients with meningitis. Another point of interest is also the fact that the penicillin gets into the spinal canal more readily in the presence of meningitis than it does when the meninges are normal.

It is evident from the three cases reported that large initial doses of sulfonamide and penicillin, intravenously with intramuscularly, will give good results. A number of intraspinal treatments may be necessary only in selected patients. This intraspinal medication does not have to be repeated as frequently as previously practiced

In our first child there were twelve spinal taps done; in the second, four; and in the last one, two Apparently the larger dosage of the drugs in the third case were quite effective, so that intrathecal therapy was not necessary Some experience during the past three years resulted in a change of our attitude concerning diagnostic and therapeutic spinal punctures. There is no doubt that unless spinal taps are carefully done there is an element of danger of injury to the intravertebral disc by the needle and also by introducing infection into the spinal canal. Greater danger lies in the possibility of irritation caused to the meninges by the penicillin, since it has been shown repeatedly that the drug acts as an irritant to the blood vessels when given intravenously. Indiscriminate cisternal taps to introduce penicillin into the cranial cavity may result in injury to the medulla by accidental puncture. As a rule, the duty of performing these taps is turned over to hospital interns who early in their career lack the experience necessary to perform punctures with precision. It is a common experience to see a child punctured a number of times before a successful tap is performed. This done each day, or twice a day as suggested by some, would eventually result either in cellulitus or reinfection in the spinal canal.

SUMMARY

Three patients with pneumococcic meningitis were cured with combined penicillin and sulfonamide therapy.

Because of a host of possible complications from multiple spinal taps, emphasis is placed on a minimum number of diagnostic and therapeutic punctures.

REFERENCES

1. Schaffer, A. J.: Med. Clin. of North America, 25: 495 (March) 1941.
2. Keefer, C. S.: West. J. Surg., 53: 93 (April) 1945.
3. Hodes, H. L., Smith, M. H., and Ickes, H. J.: J. A. M. A., 121: 1334 (April 24) 1943.
4. Hogg, P., and Bradley, C. D.: J. Ped. 26: 306 (April) 1945.
5. Hoyne, A. L.: Miss. Valley Med. J. (January) 1944.
6. Flippin, H. F.: Del. St. Med. J. 17: 37 (March) 1945.
7. Waring, A. J., Jr., and Smith, M. H.: J. A. M. A. 126: 418 (October 14) 1944.
8. Hutchins, G., and Daviees, J. A. V.: J. Ped. 27: 505 (December) 1945.

MUTILATION OF THE PENIS

JOHN P. ADAMS, M. D.*
Wilmington, Del.

Incarceration of the penis does not occur very often. Recently, Hoffman and Colby[1] summarized 114 instances in a bibliography covering 190 years. The addition of another report is only warranted by the uncommon outcome: amputation of the glans of the penis.

A three year old white boy was brought to the dispensary by his mother. The child's health has always been good except for "nervousness" which, according to the mother, manifested itself by extreme restlessness in bed. When the child was one year old it would jump in bed for two or three hours every night until sleeping ensued. The boy sleeps with his fourteen year old sister who has long blond hair and who frequently combs her hair in bed. On several occasions the mother has removed long blond hairs which were wrapped around the patient's penis.

Approximately three weeks before admission to the out-patient clinic of the hospital the boy complained of pain at attempts to void. The mother noticed marked swelling of the end of the child's penis. The urinary stream was greatly diminished and occasionally there was only scant dribbling at urination. The mother could find no constricting bands of any type about the penis. She took the boy to a physician who without examination of the boy prescribed frequent warm tub-baths.

About one week prior to the child's admission the mother noticed that the child would splatter urine over his clothing and that the urine came out of both the end of his penis

* Intern, Wilmington General Hospital.

and from the region just behind the glans. The mother noticed for the first time that the end of the penis was black.

On admission (12-7-45) the glans penis was markedly swollen and black in color. Just beyond the corona there was a constricting band composed of eight to ten fine blond hairs. The penis had been severed completely except for the dorsal portion of the urethra. A probe could be passed from the meatus back

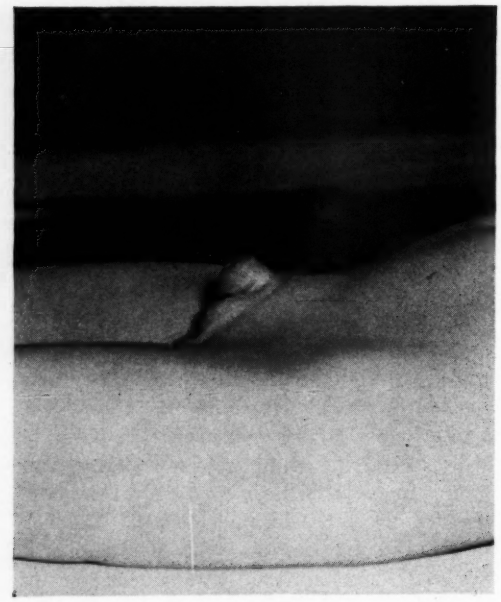

Fig. 1—The appearance of the penis five weeks after removal of the glans penis.

to the area where the urethra had been severed. The constricting band was removed and the patient was given cool boric acid soaks. The following day the penis appeared more gangrenous than before and a bleb lcm. in diameter was present on the left lateral surface of the glans. At this time it was deemed advisable to remove the gangrenous portion of the penis, which was performed by Dr. Lang W. Anderson.

Since this operation the patient has had no difficulty in urinating and has not complained of dysuria. The wound healed well.

In the majority of patients restoration of the organ is possible. In our child, the process advanced to such a state that amputation of the glans was almost completed on admission to the Hospital.

"With infants and children the difficulty results usually from the tying of strings or hairs around the penis by their caretakers in an effort to overcome enuresis."[1] In our patient this does not seem probable; other possibilities have to be considered. The mother does not believe that the boy wrapped the hairs around the penis himself or that the fourteen year old sister or other siblings did so. She attributes the tragic incident to the childs' restlessness in bed. However, the possibility of auto- or hetero-erotic manipulation cannot be excluded with certainty.

REFERENCE

1. Hoffman, H. A., and Colby, F. H.: Incarceration of the Penis, J. Urol. 54: 391, 1945.

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W. W. Bauer, M.D.
Director, Bureau of Health Education
American Medical Association

TYPHOID FEVER *

* * * *

ABSTRACT OF CASE 1.

DR. SAMUEL N. DULIN: A 29-year-old colored male was admitted to the hospital complaining of fever and cough. The patient was disoriented and irrational. Although he was being admitted for the first time he stated that he had been in the hospital for the past 60 days. That night he dressed and left the hospital without the knowledge of his attendants. The police found him several blocks away: he stated that he left because the boss gave him the afternoon off. He was not violent at any time and quietly returned to the hospital.

The abnormal findings on physical examination were a frequent cough productive of about one teaspoonful of yellow muco-purulent material, inflammation of the pharynx and tonsils, and numerous coarse, squeaking rales on inspiration and expiration throughout the chest. On admission the temperature was 100°, the pulse 84 and respiration rate 22, and the blood pressure 110/70. The following day the temperature increased to 103.6° and remained elevated thereafter; the pulse rate dropped to 72.

The laboratory findings of interest were a white blood cell count of 5,600; a hemogram of 5% stab cells, 64% mature neutrophiles, 26% lymphocytes, 2% monocytes, and 3% eosinophiles; a strongly positive reaction for albumin in the urine; and a blood urea nitrogen of 50 mg%. A spinal fluid examination was entirely negative. The clinical picture called for further laboratory tests, which led to the diagnosis.

The patient was discharged in good health after a month of hospitalization.

DISCUSSION (Conclusion)

Question: What was the result of the Wassermann test?

Answer: Serologic reactions for syphilis were negative.

Question: What was the result of sputum examination?

Answer: The examination did not render any significant information.

Question: What was the result of the Widal test?

Answer: The agglutination tests were negative a day after admission but became positive in the second week.

Question: What was the result of the blood culture?

Answer. The blood culture led to the correct diagnosis; a pure culture of E. typhosa was obtained.

ABSTRACT OF CASE 2.

DR. SAMUEL N. DULIN: A five-year-old white, Jewish girl was admitted to the hospital complaining of listlessness.

One week prior to admission her mother noticed that the child was less active than usual and that she sat around the house instead of playing. The child did not have any complaints, but her apathy alarmed the mother. Two days before admission, she complained of slight generalized abdominal pain, and vomited four times a few minutes after eating.

Before the present illness the child's health had been good; she never had any contagious diseases. She had been immunized for small pox and pertussis.

On physical examination the only abnormal findings were a muco-purulent discharge, and a tender, palpable spleen. On admission the temperature was 101°, the pulse 130, and the respiration 30. The next day, however, the temperature was 105° and remained elevated.

Laboratory examination revealed a white blood cell count of 10,500, a hemogram with 7% stab cells, 42% mature neutrophiles, 44% lymphocytes, and 7% monocytes. In the urine there was a trace of albumin, and 2 to 5 red blood cells per high-power field. The clinical findings prompted further laboratory tests which led to the diagnosis. The patient was discharged in good health after one month of hospitalization.

DISCUSSION (Conclusion)

Question: Is this another case of typhoid and, if so, how has the diagnosis been established?

Answer: It is another case of typhoid fever, and the diagnosis was again reached by blood culture. At the same time the Widal test was already positive. Stool cul-

* From the Wilmington General Hospital staff meeting, November 12, 1945.

tures were strongly positive from the third week on in both patients, while urine cultures remained negative.

Question: Was the diazo reaction positive?

Answer: No, the diazo reaction and the urochromogen test as well were negative in both patients. However, these tests may not have been properly timed.

Question: Did the patients have the odor characteristic of typhoid fever?

Answer: No. However, the art of diagnosis by such features as smell of certain diseases has been largely lost due to the infrequency of such diseases. One of the patients was a colored man, and the odor is supposedly less distinct in the Negro race.

Question: Was there a typical roseola?

Answer: No, in neither of the two patients were there any skin manifestations.

CLINICO-PATHOLOGIC DISCUSSION

DR. O. J. POLLAK: There is hardly a disease more extensively discussed in textbooks than typhoid fever. There is, however, hardly a disease with more deviations from the classical picture.

The prodromal symptoms of headache, backache, fatigue and step by step ascending temperature may be absent. The onset, which is mostly slow, might be sudden and accompanied by delirium, as in our first patient. The bradycardia is not absolute but only relative in comparison with the increase in temperature. It is not always established and especially frequently absent in children, as was the case in our second patient. Infantile and senile typhoid fever may present moderate signs and symptoms; in the aged patient splenomegaly may be absent. The roseola, which in the majority of patients is localized, may be generalized in abortive forms. The dry coated tongue with free edges may or may not be present. Constipation is just as frequent as the usually over-emphasized diarrhea. The meteorism is not characteristic; the "abdominal" facial expression only if paired with a slow pulse. Ambulatory forms of typhoid fever do not have a characteristic temperature curve. Leukopenia and lymphocytosis are the most constant features of the disease. The absence of eosinophilic cells is held characteristic for typhoid fever, but eosinophiles may be present in patients infected with parasites. The diazo and urochromogen reactions are of no value when negative and only of limited value when positive. Widal's agglutination test may be positive due to previous illness or vaccination. It remains negative in the asthenic form of typhoid, to turn positive during convalescency.

The number of diseases from which one has to differentiate typhoid fever is great. The differential diagnosis must be based on correlation of the clinical features with a host of laboratory tests. The importance of blood cultures, which in both our patients led to the diagnosis, must be emphasized.

The variety of complications encountered in typhoid fever is very large and so is the number of post-typhoid states. Relapse, recurrence, autoinfection and reinfection play an important role. Carriers of typhoid microbes may turn into excretors of the microorganisms and endanger other people.

EPIDEMIOLOGIC DISCUSSION

DR. A. PARKER HITCHENS: There are various epidemiologic aspects to typhoid fever. On the part of the medical profession the prompt reporting of any new instance of the disease to the Health Department is most important. On the part of the public and the law-maker the constant improvement of the water supply, the prohibition of the sale of raw milk, and the extermination of flies must be stressed. The Health Department's function is the tracing of infection to its source, and the finding and control of carriers.

Some progress has been made in the search for carriers by the discovery and use of a third antigen of the typhoid bacteria. Beside the somatic O-Antigen and the flagellar H-Antigen there is a Vi-(virulent) Antigen which indicates the presence of live microorganisms. Agglutination tests in convalescence and in persons suspected to be typhoid carriers should be done with all three antigens, and the agglutination with the Vi strain should serve as a screening test. Such tests should be made obligatory for food handlers and the related professions.

The investigation of the two presented pa-

tients led to discovery of the source of infection in the child. The child's grandmother had been declared a typhoid carrier fifteen years ago, and her stool culture was positive for E. typhosa at the same time our patient was at the hospital with typhoid fever. The old lady is known to have infected one son, two daughters, and two granddaughters with the same disease during these years. A number of typhoid carriers remain undetected. It is, however, equally regrettable if a known carrier spreads the disease.

HAIL AND FAREWELL

On this, the third anniversary of the beginning of the DELAWARE CHRONICLE, we must remind you that when the first issue came off the press, letters poured in asking that this little brain-child be fostered, nourished, and sustained. We then made the promise to keep it alive for the duration of the war. That period of our history is now over—in its more marked phases. A goodly number of the men and women, members in former days of the Delaware Hospital Staff, are returning. We are happy to see them. A number are still in National Service, many of them still helping to make our motto true—"We Cover the Earth." Those who are still away have been moved about so rapidly that our address list is essentially obsolete, so, reluctantly, we must say—farewell. It has been a lot of fun to keep this publication going, but more satisfying were your letters of commendation, praise, and requests for more. Your letters were unanimous in expressing the thought that the CHRONICLE, was a great little morale builder to those far from home. We heard very few criticisms, and those few were constructive. Your letters were newsy, informative, and interesting. Honors at home came our way. The Delaware State Medical Journal and the public press gave approving nods. The State of Delaware requested a complete file to be placed in the State Archives—"as an example of what was done for people of Delaware in National Service." To you who were, and to those who still are in Service, as well as to those of us who remained at home, we hope that our feeble attempts at humor left no one offended—it was all in fun. To our friends at home who helped make this venture possible—those who wrote articles for publication, to our many purchasers at "one thin dime per copy" and contributors who made this paper possible financially, to the Record Room Staff for their aid in mimeographing—to these go our deepest thanks.

And so with this issue we come to the parting of the ways—on this third birthday of the CHRONICLE, at this Christmas time, at this joyful time of the year, we sorrowfully pull our cloak about us and say to all our friends—

HAIL AND FAREWELL

E. A. U.

SAFER SULFONAMIDE MEDICATION

The dangers of toxic reactions to the kidneys and crystal formation in the urine, frequently seen when sulfathiazole or sulfadiazine is administered, has been greatly reduced by the application of a recently discovered phenomenon that the total toxic and crystallizing properties of a combination of two sulfonamides would be no greater than the toxic and crystallizing properties of one of them in the combination.

Proven by clinical trial, this means that the incidence of kidney toxicity and urine crystal formation with a combination of sulfathiazole and sulfadiazine would be very much less than if an equivalent amount of sulfathiazole or sulfadiazine were administered singularly. At the same time, the clinical therapeutic results in all conditions ameliorable to sulfadiazine or sulfathiazole therapy is often higher with the combination.

Combinations of sulfathiazole and sulfadiazine, known as Combisul-TD are now produced by the Schering Corporation of Bloomfield, N. J. For the safer treatment of meningitis, Combisul-DM, a combination of sulfadiazine and sulfamerazine is likewise available.

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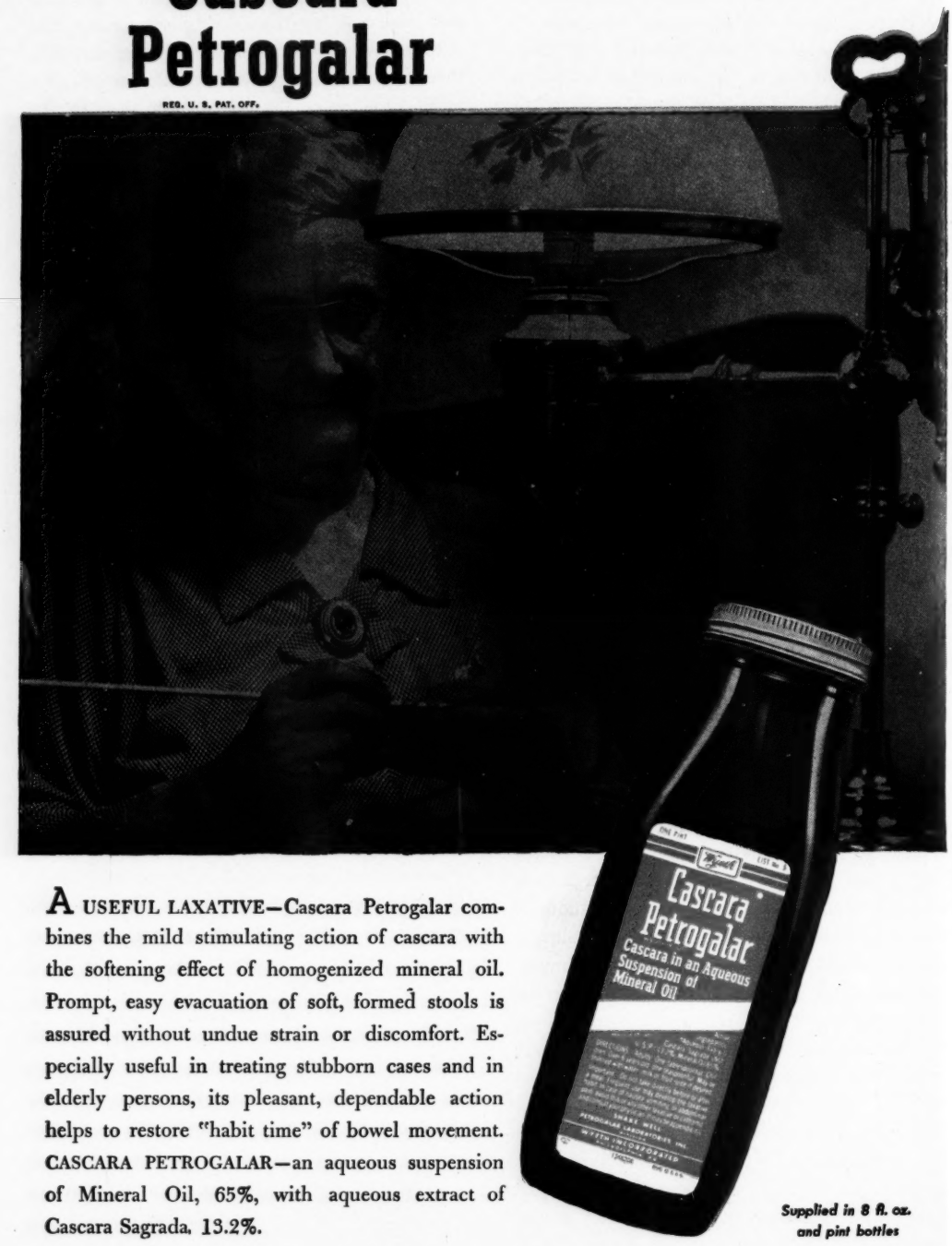

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BACKGROUND OF S-1050*

Speaking of the background of the 1945 version of the Wagner-Murray-Dingell bill, Mr. George P. Farrell, Director of the Bureau of Medical Care Insurance, Medical Society of the State of New York, had this to say:

"Most of us think the bill is a product of the social reformers of this country. However, the bill is revealed as a product of the International Labor Organization. The interlocking of national with international groups interested in social reform (including socialized medicine) had its start at the Arbitration Court of the Hague in 1899. It received official status as a private agency in Basel, Switzerland, in 1919. Under Part XIII, of the Versailles Treaty, it achieved official status as a subsidiary of the League of Nations. It moved its headquarters from Geneva, Switzerland, to Montreal at the beginning of World War II; it maintains a branch office in Washington, D. C. The original founders were the International Association for Labor Legislation and its various national affiliates. Other international organizations interlocking directorates lent needed assistance and among these was the international Association for Social Security which openly advocated the socialization of all human endeavor.

"When did this country become involved in it? In 1919 the U.S. Senate specifically withheld the assent of the United States from Part XIII of the Versailles Treaty. Samuel Gompers, President of the American Federation of Labor, had withdrawn from the American Association for Labor Legislation and denounced it as un-American. Despite senatorial skepticism about International Labor Organization's aims, however, the first officially approved International Labor Conference was held in Washington in December that same year. In 1934, through an unheralded joint resolution, passed by Congress, the United States became a member of the International Labor Organization and accepted the International Labor Organization's constitution.

"What is its purpose? It states its purpose as being "to promote social justice in all the countries of the world." To this end it collects facts about labor and social conditions, formulates international standards, and supervises their national application. In seeking to supervise the national application of International Labor Organization standards, the International Organization is obviously more than a mere fact-finding group."

The International Labor office acts as a secretariat, an information center, and a publishing house. It is staffed by experts drawn from many different countries whose knowledge, experience, and advice are available to all the nations which are members of the organization. For medical care planning there are at least three Americans among this group of experts: Chairman of the Social Security Board, Director of the Social Security Board's Bureau of Research and Statistics,

* The revised bill is S-1606.

and its assistant director. None of them are physicians.

In 1943 and 1944 the International Labor Organization put finishing touches on one hundred fourteen proposals for the "improvement and unification of medical care services." Many of these are embodied in the Wagner-Murray-Dingell Bill . . . .

Too few physicians, we think, are sufficiently detached from the overwhelming burden of the day's work and evening meetings to interest themselves in research into world-wide movements which are now affecting the status of the medical profession both here and abroad. It is the function of editorial staffs to collate available material bearing on this subject and to present it in as abbreviated form as possible in the hope that it will be noted and used in forming judgments and attitudes toward currently proposed changes in status of the profession. We are possibly too much occupied with details and thereby miss the significance of the forces at work at the national and international levels. Some of these forces have their roots in the revolt of the masses of the people against poverty, insecurity, and political tyranny, against bad working conditions, discrimination exploitation, neglect, against disease as a cause of personal suffering and as an economic hazard. Revolt against any of these conditions, which are common to all peoples in greater or less degree, has constantly occurred in the past but in a somewhat localized, restricted sense. However, with the recent increase in industrialization of many nations, hastened in some cases by war revolt has become simultaneous and additive. The resultant stresses no longer involve isolated plants or communities but now whole industries, the political life of nations, and the destiny of all peoples of the earth.

Medicine, touching all phases of human endeavor, all human life at one time or another, must necessarily be part of this revolt. More and more the irresistible tide will touch and affect the professional and economic life of each physician. The Congress and the people of the nation have thrown in their lot with the United Nations Organization and the establishment of a workable world government already is beginning to emerge. To say that this trend in world affairs and our participation in it will leave the practice of medicine here or anywhere unchanged would be to ignore the prime role which medical science must play in the postwar world. Starvation, systematic and deliberate wreckage of the health of millions of all nationalities will seriously affect the economy of many nations for generations to come.

We are fortunate in the United States to have escaped the catastrophe that has been visited upon Europe and many other parts of the world. Here there is time for considered, carefully planned change in methods for better distribution of medical care, for the creation of a demand for voluntary sickness insurance and the satisfaction of that demand, for higher quality medical service for war veterans, for more and better hospital facilities. There is no reason why a rapid, ill-considered change in types of medical service *here* should be advocated by anyone.

We can appreciate that in Europe, in Great Britain, in the Orient the urgency of necessity may be the governing factor in provoking more rapid procedures, more violent reaction to intolerable living conditions. In our own situation there seems to be little excuse for blindly plunging into government-controlled medical practice. On the contrary, there exists every opportunity and facility in this nation for intelligent experimentation with and evolutionary development of a wide variety of medical service suited to the temperament and economy of the people.

Editorial, *N. Y. S. J. M.*, Feb. 15, 1946.

Prize Contest

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons Foundation announces that the annual prize contest will be conducted again this year. For information address Dr. Jas. R. Bloss, Secretary, 418 11th Street, Huntington 1, W. Va.

BOOK REVIEWS

General and Plastic Surgery: with Emphasis on War Injuries. By J. Eastman Sheehan, M. D., Professor of Plastic Reparative Surgery, New York Polyclinic Medical School. Pp. 345, with 496 illustrations. Cloth. Price, $6.75. New York: Paul B. Hoeber, Incorporated, 1945.

This is a comparatively small book, the sixteen chapters being short. As would be expected, the major space is devoted to plastic surgery. This is not a textbook of general or plastic surgery, in the generally accepted sense, but in both fields represents the points of special interest or value that have impressed the author, and while it is not intended to be voluminous, it is in fact full of information that would require extensive reading in many books to duplicate. The illustrations are definitely helpful. The emphasis throughout is on war wounds, but the techniques apply equally well to civilian conditions. It is the author's hope that the lessons learned on the battlefield will be remembered in civilian practice. His book will do much to bring this about—we heartily recommend it.

Diseases of the Nose, Throat and Ear. Edited by Chevalier Jackson, M. D., and Chevalier L. Jackson, M. D., Honorary Professor, and Professor of Broncho-Esophagology, respectively, Temple University. With the collaboration of 64 outstanding authorities. Pp. 844, with 934 illustrations on 581 figures, including 18 plates in color. Cloth. Price, $10.00. Philadelphia: W. B. Saunders Company, 1945.

This book presents the various phases of modern otorhinolaryngology and bronchoesophagology in a form most practical for those interested in these specialties. The collaborators are all thoroughly acquainted with their respective subjects.

The articles on aviation otolaryngology and chemotherapy in otolaryngology are well prepared and of particular interest to the specialist.

The chapters on modern functional hearing tests and those on the audiometer and the fitting of hearing aids have been brought up to date and will be of especial interest to the modern otologist. Parts four and five, which include the larynx, trachea, and bronchi, have been prepared especially by the two Jacksons, and are interesting reading, and the diseases and treatment of these organs have been brought up to date. They include a number of illustrations, eighteen of which, are in full color reproduction.

This book should be well received by both students and specialists in ear, nose and throat diseases.

Men Without Guns. Text by De Witt Mackenzie, War Analyst of the Associated Press; Descriptive Captions by Major Clarence Worden, Medical Department, U. S. Army; Foreword by Major General Norman T. Kirk, Surgeon General, U. S. Army. Pp. 152, with 177 drawings, including 118 plates in full color. Cloth. Price, $5.00. Philadelphia: Blakiston Company, 1945.

This book records the great work of the Army Medical Corps in the war. It is an authentic story of the men who fought without guns to save human life, the story of the services of our doctors, nurses, and enlisted men on the battlefields and in the hospitals of Europe and Asia. Mackenzie, whose graphic recital of the story behind the pictures in the book will hold the reader's attention from beginning to end, was a war correspondent in World War I and, as Associated Press War Analyst during World War II, covered the African, European, Burma, China and Pacific fronts, where he saw the Army Medical Corps in action. A dozen famous American artists braved the hardships and perils of war to make the notable series of historical paintings reproduced from the Abbott Collection of Paintings, now the property of the U. S. Government. The book constitutes an authentic and valuable contemporary history of Army Medicine in the war and a priceless and archival treasure.

The Care of the Aged (Geriatrics). By Malford W. Thewlis, M. D., Attending Specialist, U. S. P. H. Hospitals, New York City. Fifth edition. Pp. 500, with 65 illustrations. Cloth. Price, $8.00. St. Louis: C. V. Mosby Company, 1946.

The new edition of Thewlis' popular book includes much additional recent material, twelve new sections appearing for the first time, all stressing preventive geriatrics. There is also considerable rearrangement, alterations increasing the value of the book. Treatment is given the space and importance it deserves. Geriatrics is now a recognized specialty, and we consider Thewlis' book the best in this newest specialty.

Howell's Textbook of Physiology: Edited by John F. Fulton, M. D., Sterling Professor of

Physiology, Yale University School of Medicine. Fifteenth edition. Pp. 1304, with 507 illustrations. Cloth. Price, $8.00. Philadelphia: W. B. Saunders Company, 1946.

After a lapse of six years but of less than one year after Dr. Howell's death appears the fifteenth edition of America's first textbook of physiology. Many new chapters appear and several others have been rewritten in order that the text shall include the results of the very latest researches. Dr. Howell himself, almost 85 years of age, took the keenest interest in this last edition of his renowned opus. The 24 contributors have evolved a text of uniformly pleasing style, though our feeling is that it falls a bit short of the eloquence of the old maestro. Our further feeling is that this new Howell is still America's greatest textbook of physiology.

Mitchell-Nelson. Textbook of Pediatrics. Edited by Waldo E. Nelson, M. D., Professor of Pediatrics, Temple University School of Medicine, with the collaboration of forty-nine contributors. Fourth edition. Pp. 1350, with 519 illustrations on 333 figures, in color. Cloth. Price $10:00. Philadelphia: W. B. Saunders Company, 1945.

As the editor states, "This textbook of pediatrics is the successor to the Griffith and Mitchell text and as such represents the fourth edition of the single volume series, each of the first two editions having been published in two volumes." It will be recalled by those who knew them that the death of Dr. Griffith occurred one month after that of Dr. Mitchell, in 1941. Dr. Nelson had been closely associated with Dr. Mitchell in Cincinnati.

Dr. Nelson further states in his preface: "This book has been completely rewritten and to all intents and purposes it is a 'new' book. There is some alteration in the general arrangement, a number of new sections have been added, and some of the sections of the last editions have been completely discarded. In an attempt to bring together in a single volume the representative thought on the various problems of pediatrics we have asked specially qualified persons to prepare material for a great part of the book."

This book is very comprehensive. It dwells upon practically every phase of clinical pediatrics in proportion to its importance. The reader is given a good perspective of the pediatric problem.

The illustrations and figures are excellent. The whole set-up of the book is very commendable, and this includes the size of type, the quality of paper used, and the binding. Flexibility permits the pages of the book to remain flat at whatever point it is opened.

This book is outstanding in its field and should be in the hands of every student and practitioner of pediatrics.

American Red Cross First Aid Textbook. Revised edition of 1945. Pp. 254, with 264 illustrations. Price: Paper, 60 cents; cloth, $1.00. Philadelphia: Blakiston Company, 1945.

Everybody knows of these A. R. C. First Aid books—they have appeared ever since 1909 and many millions of copies of previous editions have been used throughout the United States.

The present edition is an entirely new book prepared according to a wholly different plan. The chapters are reduced from fourteen to twelve and rearranged; the illustrations increased from 114 to 264; the style has grown in dignity and simplicity; and the scientific accuracy reaches a new maximum. This is the best A. R. C. First Aid Textbook that we have seen. This book represents a consensus of the leading surgeons and other specialists in the United States concerned with problems of first aid. The appropriate committees of the Division of Medical Sciences of the National Research Council participated in the work.

The Romance of Human Architecture. By Maurice Chideckel, M. D. Pp. 107. Cloth. Price, $2.00. Boston: Bruce Humphries, Incorported, 1945.

This little book is an anatomy and physiology for the laiety. Written in a style much superior to that found in most such books, the information is accurately and concisely imparted. There are no illustrations, for which we are grateful: the illustrations usually poured into similar books are generally ghastly things that detract from and cheapen the book. Also there is no index, which is to be regretted, for the layman may have considerable difficulty in finding a particular paragraph by looking over the table of contents. Even so, for its purpose, the book can be recommended.